TITLE OF THE INVENTION

21-HETEROCYCLIC-4-AZASTEROID DERIVATIVES AS ANDROGEN RECEPTOR MODULATORS

FIELD OF THE INVENTION

The present invention relates to 21-benzimidazole-4-azasteroid and 21-azabenzimidazole-azasteroid derivatives, their synthesis, and their use as androgen receptor modulators. More particularly, the compounds of the present invention are tissue-selective androgen receptor modulators and are thereby useful for the treatment of conditions caused by androgen deficiency or which can be ameliorated by androgen administration, such as osteoporosis, periodontal disease, bone fracture, frailty, and sarcopenia. Additionally, the SARMs of the present invention can be used to treat mental disorders associated with low testosterone, such as depression, sexual dysfunction, and cognitive decline. SARMs, being antagonists in specific tissues, are also useful in conditions where elevated androgen tone or activity causes symptoms, such as benign prostate hyperplasia and sleep apnea.

BACKGROUND OF THE INVENTION

The androgen receptor (AR) belongs to the superfamily of steroid/thyroid hormone nuclear receptors, whose other members include the estrogen receptor, the progesterone receptor, the glucocorticoid receptor, and the mineralocorticoid receptor. The AR is expressed in numerous tissues of the body and is the receptor through which the physiological as well as the pathophysiological effects of androgens, such as testosterone (T) and dihydrotestosterone (DHT), are mediated. Structurally, the AR is composed of three functional domains: the ligand binding domain (LBD), the DNA-binding domain, and amino-terminal domain. A compound that binds to the AR and mimics the effects of an endogenous AR ligand is referred to as an AR agonist, whereas a compound that inhibits the effects of an endogenous AR ligand is termed an AR antagonist.

Androgen ligand binding to the AR induces a ligand/receptor complex, which, after translocation into the nucleus of the cell, binds to regulatory DNA sequences (referred to as androgen response elements) within the promoter or enhancer regions of the target genes present in the nucleus. Other proteins termed cofactors are next recruited, which bind to the receptor leading to gene transcription.

Androgen therapy has been to treat a variety of male disorders such as reproductive disorders and primary or secondary male hypogonadism. Moreover, a number of natural or synthetic AR agonists have been investigated for the treatment of musculoskeletal disorders, such as bone disease, hematopoietic disorders, neuromuscular disease, rheumatological disease, wasting disease, and for

hormone replacement therapy (HRT), such as female androgen deficiency. In addition, AR antagonists, such as flutamide and bicalutamide, are used to treat prostate cancer. It would therefore be useful to have available compounds that can activate ("agonize") the function of the AR in a tissue-selective manner that would produce the desired osteo- and myoanabolic effects of androgens without the negative androgenic properties, such as virilization and repression of high density lipoprotein cholesterol (HDL).

The beneficial effects of androgens on bone in postmenopausal osteoporosis were documented in recent studies using combined testosterone and estrogen administration [Hofbauer, et al., Eur. J. Edocrinol. 140: 271-286 (1999)]. In a large 2-year, double-blind comparison study, oral conjugated estrogen (CEE) and methyltestosterone combinations were demonstrated to be effective in promoting accrual of bone mass in the spine and hip, while conjugated estrogen therapy alone prevented bone loss [J. Reprod. Med., 44: 1012-1020 (1999)].

Additionally, there is evidence that hot flushes decrease in women treated with CEE and methyltestosterone; however, 30% of the treated women suffered from significant increases in acne and facial hair, a complication of all current androgen pharmacotherapies [Watts, et al., Obstet. Gynecol., 85: 529-537 (1995)]. It was also found that the addition of methyltestosterone to CEE decreased HDL levels, as seen in other studies. Thus, the virilizing potential and effects on lipid profile of current androgen therapies provide a rationale for developing tissue-selective androgen receptor agonists.

Androgens play an important role in bone metabolism in men [Anderson, et al., "Androgen supplementation in eugonadal men with osteoporosis – effects of six months of treatment on bone mineral density and cardiovascular risk factors," Bone, 18: 171-177 (1996)]. Even in eugonadal men with osteoporosis, the therapeutic response to testosterone treatment reveals that androgens exert important osteoanabolic effects. Mean lumbar BMD increased from 0.799 gm/cm2 to 0.839 g/cm2, in 5 to 6 months in response to 250 mg of testosterone ester administered intramuscularly. SARMs can thus be used to treat osteoporosis in men.

Androgen deficiency occurs in men with stage D prostate cancer (metastatic) who undergo androgen deprivation therapy (ADT). Endocrine orchiectomy is achieved by long acting GnRH agonists, while androgen receptor blockade is implemented with AR antagonists. In response to hormonal deprivation, these men suffered from hot flushes, significant bone loss, weakness, and fatigue. In a pilot study of men with stage D prostate cancer, osteopenia (50% vs. 38%) and osteoporosis (38% vs. 25%) were more common in men who had undergone ADT for greater than one year than the patients who did not undergo ADT [Wei, et al., Urology, 54: 607-611 (1999)]. Lumbar spine BMD was significantly lower in men who had undergone ADT. Thus tissue selective AR antagonists in the prostate that lack antagonistic action in bone and muscle can be useful agents for the treatment of prostate cancer,

either alone or as an adjunct to traditional ADT [See also A. Stoch, et al., J. Clin. Endocrin. Metab., 86: 2787-2791 (2001)].

Tissue-selective AR antagonists can also treat polycystic ovarian syndrome in postmenopausal women. See C.A. Eagleson, et al., "Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone," J. Clin. Endocrinol. Metab., 85: 4047-4052 (2000).

SARMs can also treat certain hematopoietic disorders as androgens stimulate renal hypertrophy and erythropoietin (EPO) production. Prior to the introduction of recombinant human EPO, androgens were employed to treat anemia caused by chronic renal failure. In addition, androgens increase serum EPO levels in anemic patients with non-severe aplastic anemia and myelodysplastic syndromes. Treatment for anemia will require selective action such as can be provided by SARMs.

SARMs can also have clinical value as an adjunct to the treatment of obesity. This approach to lowering body fat is supported by published observations that androgen administration reduced subcutaneous and visceral fat in obese patients [J.C. Lovejoy, et al., "Oral anabolic steroid treatment, but not parenteral androgen treatment, decreases abdominal fat in obese, older men," Int. J. Obesity, 19: 614-624 (1995)], [J.C. Lovejoy, et al., "Exogenous Androgens Influence Body Composition and Regional Body Fat Distribution in Obese Postmenopausal Women – A Clinical Research Center Study," J. Clin. Endocrinol. Metab., 81: 2198-2203 (1996)]. Therefore, SARMs devoid of unwanted androgenic effects can be beneficial in the treatment of obesity.

Androgen receptor agonists can also have therapeutic value against metabolic syndrome (insulin resistance syndrome, syndrome X), particularly in men. Low levels of total and free testosterone and sex hormone-binding globulin (SHBG) in men have been associated with type 2 diabetes, visceral obesity, insulin resistance (hyperinsulinemia, dyslipidemia) and metabolic syndrome. D. Laaksonen, et al., Diabetes Care, 27 (5): 1036-1041(2004); see also D. Laaksonen, et al. Euro. J Endocrin, 149: 601-608 (2003); P. Márin, et al. Int. J. Obesity, 16: 991-997 (1992), and P. Márin, et al. Obesity Res., 1(4): 245-251 (1993).

Androgen receptor agonists can also have therapeutic value against neurodegenerative diseases such as Alzheimer's disease (AD). The ability of androgens to induce neuroprotection through the androgen receptor was reported by J. Hammond, et al., "Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons," J. Neurochem., 77: 1319-1326 (2001). Gouras et al. reported that testosterone reduces secretion of Alzheimer's β-amyloid peptides and can therefore be used in the treatment of AD [(Proc. Nat. Acad. Sci., 97: 1202-1205 (2000)]. A mechanism via inhibition of hyperphosphorylation of proteins implicated in the progression AD has also been described [S. Papasozomenos, "Testosterone prevents the heat shock-induced over activation of glycogen

synthase kinase-3β but not of cyclin-dependent kinase 5 and c-Jun NH_2-terminal kinase and concomitantly abolishes hyperphosphorylation of τ: Implications for Alzheimer's disease," Proc. Nat. Acad. Sci., 99: 1140-1145 (2002)].

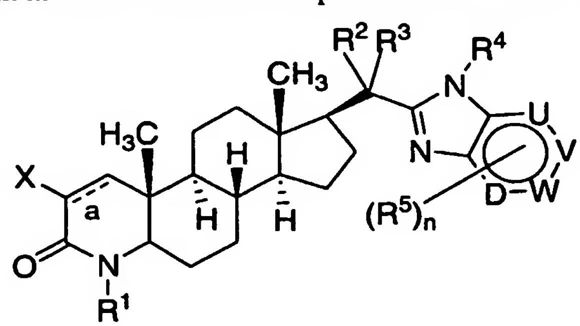
Androgen receptor agonists can also have a beneficial effect on muscle tone and strength. Recent studies have demonstrated that "physiologic androgen replacement in healthy, hypogonadal men is associated with significant gains in fat-free mass, muscle size and maximal voluntary strength," [S. Bhasin, et al., J. Endocrin., 170: 27-38 (2001)].

Androgen receptor modulators can be useful in treating decreased libido in both men and women. Androgen deficiency in men is related to diminished libido. S. Howell et al., Br. J. Cancer, 82: 158-161. Low androgen levels contribute to the decline in sexual interest in many women during their later reproductive years. S. Davis, J. Clin. Endocrinol. Metab., 84: 1886-1891 (1999). In one study, circulating free testosterone was positively correlated with sexual desire. Id. In another study, women with primary or secondary adrenal insufficiency were provided physiological DHEA replacement (50 mg/day). Compared with women taking placebo, DHEA-administered women showed an increase in the frequency of sexual thoughts, interest, and satisfaction. W. Arlt, et al., N Engl. J. Med. 341:1013-1020 (1999), see also, K. Miller, J. Clin. Endocrinol. Metab., 86: 2395-2401 (2001).

Additionally, androgen receptor modulators may also be useful in treating cognitive impairment. In a recent study, high-dose oral estrogen either alone or in combination with high-dose oral methyltestosterone was given to postmenopausal women for a four-month period. Cognitive tests were administered before and after the four-month hormone treatment. The investigation found that women receiving a combination of estrogen (1.25 mg) and methyltestosterone (2.50 mg) maintained a steady level of performance on the Building Memory task, but the women receiving estrogen (1.25 mg) alone exhibited decreased performance. A. Wisniewski, Horm. Res. 58:150-155 (2002).

SUMMARY OF THE INVENTION

The present invention relates to compounds of structural formula I:



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or a pharmaceutically acceptable salt or stereoisomer thereof, their uses and pharmaceutical compostions.

These compounds are effective as androgen receptor agonists and are particularly effective as SARMs. They are therefore useful for the treatment of conditions caused by androgen deficiency or which can be ameliorated by androgen administration.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

In this invention, we have identified compounds that function as SARMs using a series of in vitro cell-assays that profile ligand mediated activation of AR, such as (i) N-C interaction, (ii) transcriptional repression, and (iii) transcriptional activation. SARM compounds in this invention, identified with the methods listed above, exhibit tissue selective AR agonism in vivo, i.e. agonism in bone (stimulation of bone formation in a rodent model of osteoporosis) and antagonism in prostate (minimal effects on prostate growth in castrated rodents and antagonism of prostate growth induced by AR agonists).

The compounds of the present invention identified as SARMs are useful to treat diseases or conditions caused by androgen deficiency which can be ameliorated by androgen administration. Such compounds are ideal for the treatment of osteoporosis in women and men as a monotherapy or in combination with inhibitors of bone resorption, such as bisphosphonates, estrogens, SERMs, cathepsin K inhibitors, $\alpha v\beta 3$ integrin receptor antagonists, calcitonin, and proton pump inhibitors. They can also be used with agents that stimulate bone formation, such as parathyroid hormone or analogs thereof. The SARM compounds of the present invention can also be employed for treatment of prostate disease, such as prostate cancer and benign prostatic hyperplasia (BPH). Moreover, compounds of this invention exhibit minimal effects on skin (acne and facial hair growth) and can be useful for treatment of hirsutism. Additionally, compounds of this invention can stimulate muscle growth and can be useful for treatment of sarcopenia and frailty. They can be employed to reduce visceral fat in the treatment of obesity. Moreover, compounds of this invention can exhibit androgen agonism in the central nervous system and can be useful to treat vasomotor symptoms (hot flush) and to increase energy and libido. They can be used in the treatment of Alzheimer's disease.

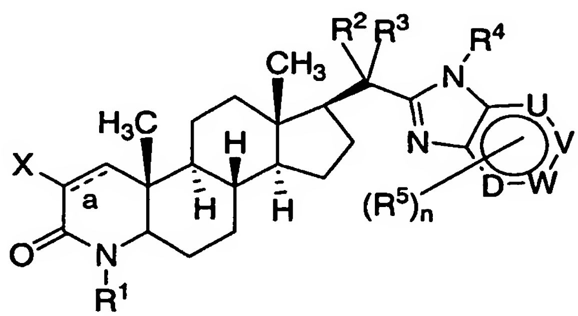
The compounds of the present invention can also be used in the treatment of prostate cancer, either alone or as an adjunct to GnRH agonist/antagonist therapy, for their ability to restore bone, or as a replacement for antiandrogen therapy because of their ability to antagonize androgen in the prostate, and minimize bone depletion. Further, the compounds of the present invention can be used for their ability to restore bone in the treatment of pancreatic cancer as an adjunct to treatment with antiandrogen, or as monotherapy for their antiandrogenic properties, offering the advantage over traditional antiandrogens of being bone-sparing. Additionally, compounds of this invention can increase the number of blood cells, such as red blood cells and platelets, and can be useful for the treatment of

hematopoietic disorders, such as aplastic anemia. Thus, considering their tissue selective androgen receptor agonism listed above, the compounds of this invention are ideal for hormone replacement therapy in hypogonadic (androgen deficient) men.

This invention is also concerned with safely and specifically treating a male subject with abdominal adiposity, metabolic syndrome (also known as the 'insulin resistance syndrome', and 'Syndrome X'), and type II diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds that are useful as androgen receptor modulators, in particular, as selective androgen receptor modulators. Compounds of the present invention are described by structural formula I:



I

a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

a is chosen from a double bond and a single bond;

X is hydrogen or halogen;

n is 0, 1, 2, 3, or 4;

U, V, W, and D are each independently chosen from CH, and N, provided that at least one of U, V, W, and D is CH;

R^1 is chosen from hydrogen, CF_3, carbonyl(C_{1-3} alkyl), hydroxyl, C_{1-4} alkoxy, halogen, C_{1-3} alkyl, hydroxymethyl, and (C_{0-6} alkyl)$_2$amino, wherein said alkyl and alkoxy are each optionally substituted with one to seven fluorine atoms;

R^2 and R^3 are each independently chosen from: hydrogen, halogen,C_{1-8} alkyl, amino C_{0-6}alkyl, C_{1-6} alkylamino C_{0-6}alkyl, (C_{1-6} alkyl)$_2$amino C_{0-6}alkyl, C_{1-6} alkoxy C_{0-6}alkyl, hydroxycarbonyl C_{0-6}alkyl, hydroxy C_{0-6}alkyl, C_{1-6} alkoxycarbonyl C_{0-6}alkyl, hydroxycarbonyl C_{1-6} alkyloxy, cyano, perfluoroC_{1-4}alkyl, perfluoroC_{1-4}alkoxy, C_{0-6} alkylcarbonyl,

C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6}alkylaminocarbonylamino, $(C_{1-6}alkyl)_2$ aminocarbonylamino, and $(C_{1-6}alkyl)_2$ aminocarbonyloxy,

and wherein

R^2 and R^3 together with the carbon atom to which they are attached can optionally form a C_{3-6} cycloalkyl group, or an oxo group, and

R^2 and R^3 are each independently optionally substituted with one or more R^6;

R^4 is chosen from: hydrogen, halogen, C_{1-10} alkyl(carbonyl)$_{0-1}$, aryl C_{0-8} alkyl, amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl, C_{1-6} alkylamino C_{0-8} alkyl, C_{1-6} dialkylamino C_{0-8} alkyl, aryl C_{0-6} alkylamino C_{0-6} alkyl, C_{1-4} alkoxyamino C_{0-8} alkyl, hydroxy C_{1-6} alkylamino C_{0-8} alkyl, C_{1-4} alkoxy C_{0-6} alkyl, hydroxycarbonyl C_{0-6} alkyl, C_{1-4} alkoxycarbonyl C_{0-6} alkyl, hydroxycarbonyl C_{0-6} alkyloxy, hydroxy C_{1-6} alkylamino C_{0-6} alkyl, or hydroxy C_{0-6} alkyl,

wherein R^4 is optionally substituted with one or more groups chosen from hydrogen, OH, (C_{1-6})alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1$-C_6 alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, $-O_{(0-1)}(C_{1-10})$perfluoroalkyl, and NH_2;

R^5 is chosen from: halogen, (carbonyl)$_{0-1}C_{1-10}$ alkyl, (carbonyl)$_{0-1}C_{2-10}$ alkenyl, (carbonyl)$_{0-1}C_{2-10}$ alkynyl, (carbonyl)$_{0-1}$aryl C_{1-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl, (C_{3-8})heterocyclyl C_{0-10} alkyl, C_{1-4}acylamino C_{0-10} alkyl, C_{0-10} alkylamino C_{0-10} alkyl, di-$(C_{1-10}$ alkyl)amino C_{0-10} alkyl, arylC_{0-10} alkylamino C_{0-10} alkyl, (arylC_{0-10} alkyl)$_2$amino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkylamino C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkylamino C_{0-10} alkyl, $(C_{3-8}$ cycloalkyl C_{0-10} alkyl$)_2$amino C_{0-10} alkyl, $(C_{3-8}$ heterocyclyl C_{0-10} alkyl$)_2$amino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl aminocarbonylamino, $(C_{1-10}$ alkyl$)_2$aminocarbonylamino, (aryl C_{1-10} alkyl$)_{1-2}$aminocarbonylamino, C_{0-10} alkyl aminocarbonylamino, C_{3-8} heterocyclyl C_{0-10} alkyl aminocarbonylamino,

$(C_{1-10}$ alkyl$)_2$aminocarbonyl C_{0-10} alkyl, (aryl C_{1-10} alkyl$)_{1-2}$aminocarbonyl C_{0-10} alkyl, C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, aryl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, $(C_{1-10}$ alkyl$)_2$aminocarbonyl, (aryl C_{1-10} alkyl$)_{1-2}$aminocarbonyl, C_{1-10} alkoxy (carbonyl$)_{0-1}C_{0-10}$ alkyl, carboxy C_{0-10} alkylamino, carboxy C_{0-10} alkyl, carboxy aryl, carboxy C_{3-8} cycloalkyl, carboxy C_{3-8} heterocyclyl, C_{1-10} alkoxy, C_{1-10}alkyloxy C_{0-10}alkyl C_{1-10} alkylcarbonyloxy, C_{3-8} heterocyclyl C_{0-10} alkylcarbonyloxy, C_{3-8} cycloalkyl C_{0-10} alkylcarbonyloxy, aryl C_{0-10} alkylcarbonyloxy, C_{1-10} alkylcarbonyloxy amino, aryl C_{0-10} alkylcarbonyloxy amino, C_{3-8} heterocyclyl C_{0-10} alkylcarbonyloxy amino, C_{3-8} cycloalkyl C_{0-10} alkylcarbonyloxy amino, $(C_{1-10}$ alkyl$)_2$aminocarbonyloxy, (aryl C_{0-10} alkyl$)_{1-2}$aminocarbonyloxy, $(C_{3-8}$ heterocyclyl C_{0-10} alkyl$)_{1-2}$aminocarbonyloxy, $(C_{3-8}$ cycloalkyl C_{0-10}alkyl$)_{1-2}$aminocarbonyloxy, hydroxy C_{0-10}alkyl, hydroxycarbonylC_{0-10}alkoxy, hydroxycarbonylC_{0-10}alkyloxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, aryl C_{0-10} alkylsulfinyl, C_{3-8} heterocyclyl C_{0-10} alkylsulfinyl, C_{3-8} cycloalkyl C_{0-10} alkylsulfinyl, C_{1-10} alkylsulfonyl, aryl C_{0-10} alkylsulfonyl, C_{3-8} heterocyclyl C_{0-10} alkylsulfonyl, C_{3-8} cycloalkyl C_{0-10} alkylsulfonyl, C_{1-10} alkylsulfonylamino, aryl C_{1-10} alkylsulfonylamino, C_{3-8} heterocyclyl C_{1-10} alkylsulfonylamino, C_{3-8} cycloalkyl C_{1-10} alkylsulfonylamino, cyano, nitro, perfluoroC_{1-6}alkyl, and perfluoroC_{1-6}alkoxy;

wherein R^5 is optionally substituted with at least one substituent, R^6; and

R^6 is chosen from: halogen, (carbonyl$)_{0-1}C_{1-10}$ alkyl, (carbonyl$)_{0-1}C_{2-10}$ alkenyl, (carbonyl$)_{0-1}C_{2-10}$ alkynyl, (carbonyl$)_{0-1}$aryl C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl, (C_{3-8})heterocyclyl C_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl, C_{1-4}acylamino C_{0-10} alkyl, C_{0-10} alkylamino C_{0-10} alkyl, di-(C_{1-10} alkyl)amino C_{0-10} alkyl, arylC_{0-10} alkylamino C_{0-10} alkyl, (arylC_{0-10} alkyl)$_2$amino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkylamino C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkylamino C_{0-10} alkyl, C_{3-8} heterocycloalkyl C_{0-10} alkylamino C_{0-10} alkyl, C_{0-10} alkyl carbimidoylC_{0-10} alkyl, (C_{1-10} alkyl)$_2$aminocarbonyl, C_{1-10} alkoxy (carbonyl)$_{0-1}$$C_{0-10}$ alkyl, C_{1-10}alkyloxy C_{0-10}alkyl, (C_{1-10} alkyl)$_2$aminocarbonyloxy, hydroxycarbonylC_{0-10}alkoxy, (C_{1-10} alkyl)$_2$aminocarbonyloxy, (aryl C_{0-10} alkyl)$_{1-2}$aminocarbonyloxy, hydroxy C_{0-10}alkyl, C_{1-10} alkylsulfonyl, C_{1-10} alkylsulfonylamino, aryl C_{1-10} alkylsulfonylamino, C_{3-8} heterocyclyl C_{1-10} alkylsulfonylamino, C_{3-8} heterocycloalkyl C_{1-10} alkylsulfonylamino, perfluoroC_{1-6}alkoxy, C_{3-8} cycloalkyl C_{1-10} alkylsulfonylamino, cyano, nitro, and perfluoroC_{1-6}alkyl,

wherein R^6 is optionally substituted with one or more groups chosen from: OH, NO_2, (C_{1-6})alkoxy, halogen, CO_2H, CN, O(C=O)C_1-C_6 alkyl, trifluoromethoxy, trifluoroethoxy, and $-O_{(0-1)}(C_{1-10})$perfluoroalkyl.

In one embodiment of the invention, X is fluorine.

In another embodiment, X is hydrogen.

In yet another embodiment, a is a single bond.

In another embodiment of the invention, a is a double bond.

In another embodiment, R^1 is chosen from: hydrogen, CF_3, hydroxyl, and C_{1-3} alkyl optionally substituted with one to seven fluorine atoms. In a variant of this embodiment, R^1 is chosen from: hydrogen and C_{1-3} alkyl. In yet another variant, R^1 is methyl.

In another non-limiting embodiment of the invention, at least two of U, V, W, and D are each CH. In a variant of this embodiment, at least three of U, V, W, and D are each CH. In yet another embodiment, each of U, V, W, and D are each CH.

In one embodiment of the invention, R^5 is chosen from: halogen, (carbonyl)$_{0-1}$$C_{1-10}$ alkyl, (carbonyl)$_{0-1}$$C_{2-10}$ alkenyl, (carbonyl)$_{0-1}$$C_{2-10}$ alkynyl, C_{1-10} alkenylamino, (carbonyl)$_{0-1}$aryl C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl,

(C_{3-8})heterocyclyl C_{0-10} alkyl, C_{3-8} heterocycloalkyl C_{0-10} alkyl, C_{1-4} acylamino C_{0-10} alkyl, C_{0-10} alkylamino C_{0-10} alkyl, di-(C_{1-10} alkyl)amino C_{0-10} alkyl, arylC_{0-10} alkylamino C_{0-10} alkyl, (arylC_{0-10} alkyl)$_2$amino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkylamino C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkylamino C_{0-10} alkyl, C_{3-8} heterocycloalkyl C_{0-10} alkylamino C_{0-10} alkyl, (C_{3-8} cycloalkyl C_{0-10} alkyl)$_2$amino C_{0-10} alkyl, (C_{3-8} heterocyclyl C_{0-10} alkyl)$_2$amino C_{0-10} alkyl, (C_{3-8} heterocycloalkyl C_{0-10} alkyl)$_2$amino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl aminocarbonylamino, (C_{1-10} alkyl)$_2$aminocarbonylamino, (aryl C_{1-10} alkyl)$_{1-2}$aminocarbonylamino, C_{0-10} alkyl aminocarbonylamino, C_{3-8} heterocyclyl C_{0-10} alkyl aminocarbonylamino, C_{3-8} heterocycloalkyl C_{0-10} alkyl aminocarbonylamino, C_{0-10} alkyl carbonylamino C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl carbonylamino C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkyl carbonylamino C_{0-10} alkyl, C_{3-8} heterocycloalkyl C_{0-10} alkyl carbonylamino C_{0-10} alkyl, (C_{1-10} alkyl)$_2$aminocarbonyl C_{0-10} alkyl, (aryl C_{1-10} alkyl)$_{1-2}$aminocarbonyl C_{0-10} alkyl, C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, C_{3-8} heterocyclyl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, aryl C_{0-10} alkyl aminocarbonyl C_{0-10} alkyl, carboxy C_{0-10} alkyl, C_{1-10} alkoxy (carbonyl)$_{0-1}$$C_{0-10}$ alkyl, carboxy C_{0-10} alkylamino, carboxy C_{0-10} alkyl, carboxy aryl, carboxy C_{3-8} cycloalkyl, carboxy C_{3-8} heterocyclyl, C_{1-10} alkoxy, C_{1-10}alkyloxy C_{0-10}alkyl, hydroxy C_{0-10}alkyl, hydroxycarbonylC_{0-10}alkoxy, hydroxycarbonylC_{0-10}alkyloxy, C_{1-10} alkylthio, C_{1-10} alkylsulfonyl, aryl C_{0-10} alkylsulfonyl, C_{3-8} heterocyclyl C_{0-10} alkylsulfonyl, C_{3-8} cycloalkyl C_{0-10} alkylsulfonyl, C_{1-10} alkylcarbonyloxy, C_{3-8} heterocyclyl C_{0-10} alkylcarbonyloxy, C_{3-8} cycloalkyl C_{0-10} alkylcarbonyloxy, aryl C_{0-10} alkylcarbonyloxy, aryl C_{0-10} alkyl carbonylamino C_{0-10} alkyl, amino C_{0-10} alkyl carbimidoylC_{0-10} alkylamino, C_{0-10} alkylcarboxy C_{0-10} alkylamino, C_{1-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkylamino,

C_{3-8} heterocyclyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkylamino,
C_{3-8}heterocycloalkylC_{0-10}alkyl(carbonyl)$_{0-1}$oxyC_{0-10}alkylamino,
C_{3-8} cycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkylamino,
aryl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkylamino,
C_{1-10} alkylsulfonylamino, aryl C_{1-10} alkylsulfonylamino,
C_{3-8} heterocyclyl C_{1-10} alkylsulfonylamino, C_{3-8} heterocycloalkyl C_{1-10} alkylsulfonylamino,
C_{3-8} cycloalkyl C_{1-10} alkylsulfonylamino, cyano, nitro,
perfluoroC_{1-6}alkyl, and perfluoroC_{1-6}alkoxy, and wherein R^5 is optionally substituted with at least one substituent R^6.

In one embodiment of the invention, R^2 and R^3 are each independently chosen from: hydrogen, halogen, C_{1-8} alkyl, amino C_{0-6}alkyl, C_{1-6} alkylamino C_{0-6}alkyl, C_{1-6} alkoxy C_{0-6}alkyl, hydroxycarbonyl C_{0-6}alkyl, hydroxycarbonyl C_{1-6} alkyloxy, hydroxy C_{0-6}alkyl, C_{0-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6}alkylaminocarbonylamino, and wherein R^2 and R^3 together with the carbon atom to which they are attached can optionally form a C_{3-6} cycloalkyl group, or an oxo group, and R^2 and R^3 are each independently optionally substituted with one or more R^6.

Illustrative but nonlimiting examples of compounds of the present invention are the following:

17β-(1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(7*H*-purin-8-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(1*H*-benzimidazol-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-methyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-chloro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-methoxy-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(6-methyl-7*H*-purin-8-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(1*H*-imidazo[4,5-*c*]pyridin-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-fluoro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(4-methyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-trifluoromethyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-methyl carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-[(5-carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6-chloro-5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-N, N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-N-methyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6- carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6-methyl carboxyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6-N-methyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(6-N,N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(1-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(3-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(1-ethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(1-ethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(3-trifluoroethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-methyl carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one;

17β-[(5- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-N,N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one;

20-fluoro-20-(1*H*-imidazo[4,5-*b*]pyridin-3-yl)-4-methyl-4-aza-5α-androst-1-en-3-one;

17β-[(5-fluoro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androstan-3-one; and pharmaceutically acceptable salts and stereoisomers thereof.

The compounds of the present invention can have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention.

In addition, the compounds disclosed herein can exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric

structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof. The term  represents the remainder of the 4-azasteroid derivatives of the present invention.

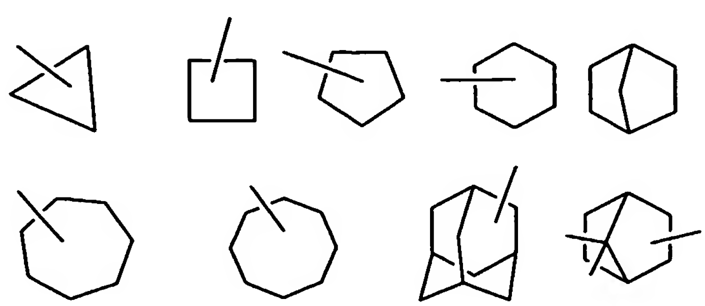
A B

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.). The term "C_0 alkyl" (as in "C_{0-8} alkylaryl") shall refer to the absence of an alkyl group.

The term "alkenyl" shall mean straight or branched chain alkenes of two to ten total carbon atoms, or any number within this range.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds can be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group can contain triple bonds and can be substituted if a substituted alkynyl group is indicated.

"Cycloalkyl" as used herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, tetrahydro-naphthalene, methylenecylohexyl, and the like. As used herein, examples of "$C_3 - C_{10}$ cycloalkyl" can include, but are not limited to:



"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

"Perfluoroalkyl" represents alkyl chains of up to 10 carbon atoms having exhaustive substitution of their corresponding hydrogens with fluorine atoms.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include, but are not limited to, phenyl, naphthyl, tetrahydro-naphthyl, indanyl, or biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms chosen from O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl.

In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appears in a name of a substituent (e.g., aryl C_{0-8} alkyl), it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_{0-8}) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl,

indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

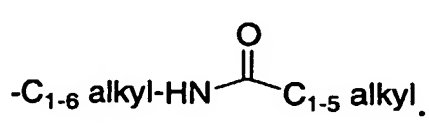
The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and include an aryl portion where aryl is as defined above. Examples of arylalkyl include, but are not limited to, benzyl, phenylethyl, phenylpropyl, naphthylmethyl, and naphthylethyl. Examples of alkylaryl include, but are not limited to, toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine and butylpyridine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" means "=O". The term "carbonyl" means "C=O."

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

When any variable (e.g., R^2, R^3, etc.) occurs more than one time in any substituent or in formula I, its definition in each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

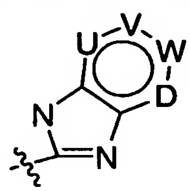
Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to



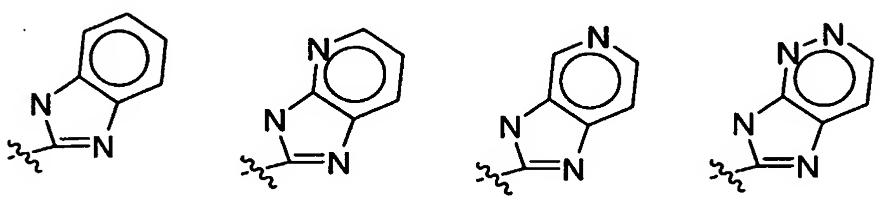
In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, R^3, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity.

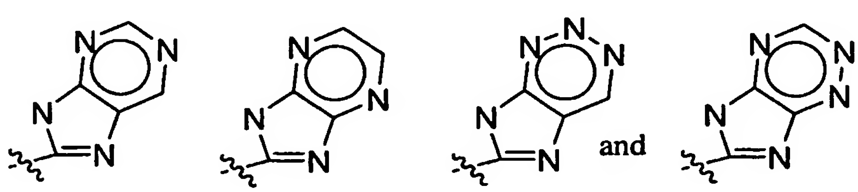
Lines drawn into the ring systems from substituents indicate that the indicated bond can be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups can be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases one embodiment will have from zero to three substituents.



can be chosen from:





In one embodiment of the invention, R^1 is chosen from hydrogen, $(C_{0\text{-}6}$ alkyl$)_2$amino $C_{0\text{-}6}$alkyl, and $C_{1\text{-}3}$ alkyl, wherein said alkyl is optionally substituted with one to seven fluorine atoms. In a variant of this embodiment, R^1 is chosen from hydrogen, CF_3, and $C_{1\text{-}3}$ alkyl. In another variant, R^1 is methyl.

In one embodiment of the invention, R^5 is chosen from: halogen, (carbonyl)$_{0-1}$C$_{1-10}$ alkyl, (carbonyl)$_{0-1}$C$_{2-10}$ alkenyl, (carbonyl)$_{0-1}$C$_{2-10}$ alkynyl, (carbonyl)$_{0-1}$aryl C$_{1-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl, (C$_{3-8}$)heterocyclyl C$_{0-10}$ alkyl, C$_{1-4}$acylamino C$_{0-10}$ alkyl, C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, arylC$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{0-10}$ alkyl aminocarbonylamino, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonylamino, C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, aryl C$_{0-10}$alkylaminocarbonylC$_{0-10}$ alkyl, C$_{1-10}$ alkoxy (carbonyl)$_{0-1}$C$_{0-10}$ alkyl, carboxy C$_{0-10}$ alkylamino, carboxy C$_{0-10}$ alkyl, carboxy aryl, carboxy C$_{3-8}$ cycloalkyl, carboxy C$_{3-8}$ heterocyclyl, C$_{1-10}$ alkoxy, C$_{1-10}$alkyloxy C$_{0-10}$alkyl, hydroxy C$_{0-10}$alkyl, hydroxycarbonylC$_{0-10}$alkoxy, hydroxycarbonylC$_{0-10}$alkyloxy, (C$_{1-10}$ alkyl)$_2$aminocarbonylC$_{0-10}$ alkyl, (aryl C$_{1-10}$ alkyl)$_{1-2}$aminocarbonyl C$_{0-10}$ alkyl, C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, aryl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, (C$_{1-10}$ alkyl)$_2$aminocarbonyl, (aryl C$_{1-10}$ alkyl)$_{1-2}$aminocarbonyl, C$_{1-10}$ alkylthio, C$_{1-10}$ alkylsulfonyl, aryl C$_{0-10}$ alkylsulfonyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkylsulfonyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylsulfonyl, C$_{1-10}$ alkylsulfonylamino, aryl C$_{1-10}$ alkylsulfonylamino, C$_{3-8}$ heterocyclyl C$_{1-10}$ alkylsulfonylamino, C$_{3-8}$ cycloalkyl C$_{1-10}$ alkylsulfonylamino, cyano, nitro, perfluoroC$_{1-6}$alkyl, and perfluoroC$_{1-6}$alkoxy. R^5 can optionally substituted with at least one substituent R^6.

In another embodiment, R^5 is chosen from: halogen, (carbonyl)$_{0-1}$C$_{1-10}$ alkyl, (carbonyl)$_{0-1}$aryl C$_{1-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl, (C$_{3-8}$)heterocyclyl C$_{0-10}$ alkyl, C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, arylC$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, C$_{0-10}$ alkyl aminocarbonylamino, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonylamino, C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, aryl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{1-10}$ alkoxy (carbonyl)$_{0-1}$C$_{0-10}$ alkyl, carboxy C$_{0-10}$ alkylamino, carboxy C$_{0-10}$ alkyl, C$_{1-10}$ alkoxy, C$_{1-10}$alkyloxy C$_{0-10}$alkyl, hydroxy C$_{0-10}$alkyl, hydroxycarbonylC$_{0-10}$alkoxy, hydroxycarbonylC$_{0-10}$alkyloxy, C$_{1-10}$ alkylthio, C$_{1-10}$ alkylsulfonyl, C$_{1-10}$ alkylsulfonylamino, cyano, nitro, perfluoroC$_{1-6}$alkyl, and perfluoroC$_{1-6}$alkoxy. Additionally, R^5 is optionally substituted with at least one substituent R^6.

In yet another embodiment of the invention, R^5 is chosen from: halogen, (carbonyl)$_{0-1}$C$_{1-10}$ alkyl, C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, aryl C$_{0-10}$ alkyl aminocarbonyl C$_{0-10}$ alkyl, C$_{1-10}$ alkoxy (carbonyl)$_{0-1}$ C$_{0-10}$ alkyl, carboxy C$_{0-10}$ alkyl, C$_{1-10}$ alkoxy, C$_{1-10}$alkyloxy C$_{0-10}$alkyl, cyano, nitro, perfluoroC$_{1-6}$alkyl, and perfluoroC$_{1-6}$alkoxy, wherein R^5 is optionally substituted with at least one substituent R^6.

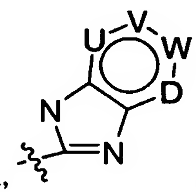
In one embodiment, R^6 is chosen from: halogen, (carbonyl)$_{0-1}$C$_{1-10}$ alkyl, (carbonyl)$_{0-1}$aryl C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl, (C$_{3-8}$)heterocyclyl C$_{0-10}$ alkyl, (C$_{3-8}$)heterocycloalkyl C$_{0-10}$ alkyl, C$_{1-4}$acylamino C$_{0-10}$ alkyl, C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, arylC$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ heterocyclyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{3-8}$ heterocycloalkyl C$_{0-10}$ alkylamino C$_{0-10}$ alkyl, C$_{0-10}$ alkyl carbimidoylC$_{0-10}$ alkyl, C$_{1-10}$ alkoxy (carbonyl)$_{0-1}$C$_{0-10}$ alkyl, C$_{1-10}$alkyloxy C$_{0-10}$alkyl, hydroxy C$_{0-10}$alkyl, C$_{1-10}$ alkylsulfonyl, C$_{1-10}$ alkylsulfonylamino, cyano, nitro, perfluoroC$_{1-6}$alkyl, and perfluoroC$_{1-6}$alkoxy, wherein R^4 is optionally substituted with one or more groups chosen from: OH, (C$_{1-6}$)alkoxy, halogen, CO_2H, CN, O(C=O)C$_1$-C$_6$ alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, -O$_{(0-1)}$(C$_{1-10}$)perfluoroalkyl, and NH_2.

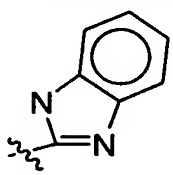
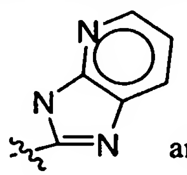
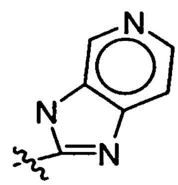
In one embodiment of the invention, R^2 and R^3 are each independently chosen from: hydrogen, halogen, C$_{1-10}$ alkyl(carbonyl)$_{0-1}$, aryl C$_{0-8}$ alkyl, amino C$_{0-8}$ alkyl, C$_{1-6}$ alkylamino C$_{0-8}$ alkyl, aryl C$_{0-6}$ alkylamino C$_{0-6}$ alkyl, C$_{1-4}$ alkoxyamino C$_{0-8}$ alkyl, hydroxy C$_{1-6}$ alkylamino C$_{0-8}$ alkyl, C$_{1-4}$ alkoxy C$_{0-6}$ alkyl, hydroxycarbonyl C$_{0-6}$ alkyl, C$_{1-4}$ alkoxycarbonyl C$_{0-6}$ alkyl, hydroxy C$_{0-6}$ alkyl, wherein R^3 is optionally substituted with one or more groups chosen from hydrogen, OH, (C$_{1-6}$)alkoxy, halogen, CO_2H, CN, O(C=O)C$_1$-C$_6$ alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, -O$_{(0-1)}$(C$_{1-10}$)perfluoroalkyl, and NH_2.

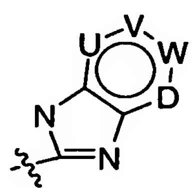
In another embodiment of the invention, R^2 and R^3 are each independently chosen from: hydrogen, halogen, C$_{1-10}$ alkyl(carbonyl)$_{0-1}$, C$_{1-6}$ alkylamino C$_{0-8}$ alkyl, C$_{1-4}$ alkoxyamino C$_{0-8}$ alkyl, C$_{1-4}$ alkoxy C$_{0-6}$ alkyl, hydroxycarbonyl C$_{0-6}$ alkyl, C$_{1-4}$ alkoxycarbonyl C$_{0-6}$ alkyl, hydroxy C$_{0-6}$ alkyl, wherein R^3 is optionally substituted with one or more groups chosen from hydrogen, OH, (C$_{1-6}$)alkoxy, halogen, CO_2H, CN, O(C=O)C$_1$-C$_6$ alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, -O$_{(0-1)}$(C$_{1-10}$)perfluoroalkyl, and NH_2.

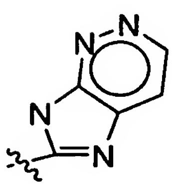
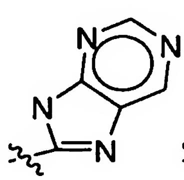
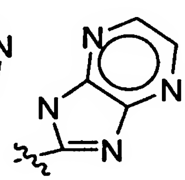
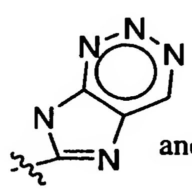
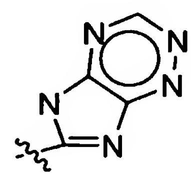
In yet another embodiment, R^2 and R^3 are each independently chosen from: hydrogen, halogen, C_{1-10} alkyl(carbonyl)$_{0-1}$, and hydroxy C_{0-6} alkyl, wherein R^3 is optionally substituted with one or more groups chosen from hydrogen, OH, (C_{1-6})alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1$-C_6 alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, $-O_{(0-1)}(C_{1-10})$perfluoroalkyl, and NH_2.

In yet another embodiment of the invention, two of U, V, W, and D are each nitrogen and the remaining two substituent ring members are carbon.

In one embodiment of the invention,  is chosen from:

  and  .

In another embodiment,  can be chosen from:

    and  .

Compounds of the present invention have been found to be tissue- selective modulators of the androgen receptor (SARMs). In one aspect, compounds of the present invention can be useful to activate the function of the androgen receptor in a mammal, and in particular to activate the function of the androgen receptor in bone and/or muscle tissue and block or inhibit ("antagonize") the function of the androgen receptor in the prostate of a male individual or in the uterus of a female individual.

A further aspect of the present invention is the use of compounds of formula I to attenuate or block the function of the androgen receptor in the prostate of a male individual or in the uterus of a female individual induced by AR agonists, but not in hair-growing skin or vocal cords, and activate the function of the androgen receptor in bone and/or muscle tissue, but not in organs which control blood lipid levels (e.g. liver).

Representative compounds of the present invention typically display submicromolar binding affinity for the androgen receptor. Compounds of this invention are therefore useful in treating mammals suffering from disorders related to androgen receptor function. Therapeutically effective amounts of the compound, including the pharmaceutically acceptable salts thereof, are administered to the mammal, to treat disorders related to androgen receptor function, such as, androgen deficiency, disorders which can be ameliorated by androgen replacement, or which can be improved by androgen replacement, including: enhancement of weakened muscle tone, osteoporosis, osteopenia, glucocorticoid-induced osteoporosis, periodontal disease, bone fracture (for example, vertebral and non-vertebral fractures), bone damage following bone reconstructive surgery, sarcopenia, frailty, aging skin, male hypogonadism, postmenopausal symptoms in women, atherosclerosis, hypercholesterolemia, hyperlipidemia, obesity, aplastic anemia and other hematopoietic disorders, pancreatic cancer, inflammatory arthritis and joint repair, HIV-wasting, prostate cancer, benign prostatic hyperplasia (BPH), cancer cachexia, Alzheimer's disease, muscular dystrophies, cognitive decline, sexual dysfunction, sleep apnea, depression, premature ovarian failure, and autoimmune disease. Treatment is effected by administration of a therapeutically effective amount of a compound of structural formula I to a mammal in need of such treatment. In addition, these compounds are useful as ingredients in pharmaceutical compositions alone or in combination with other active agents.

In one embodiment, the compounds of the present invention can be used to treat conditions in a male individual which are caused by androgen deficiency or which can be ameliorated by androgen replacement, including, but not limited to, osteoporosis, osteopenia, glucocorticoid-induced osteoporosis, periodontal disease, HIV-wasting, prostate cancer, cancer cachexia, obesity, arthritic conditions, anemias, such as for example, aplastic anemia, muscular dystrophies, and Alzheimer's disease, cognitive decline, sexual disfunction, sleep apnea, depression, benign prostatic hyperplasia (BPH), abdominal obesity, metabolic syndrome, type II diabetes, and atherosclerosis, alone or in combination with other active agents. Treatment is effected by administration of a therapeutically effective amount of a compound of structural formula I to a male individual in need of such treatment.

"Arthritic condition" or "arthritic conditions" refers to a disease wherein inflammatory lesions are confined to the joints or any inflammatory conditions of the joints, most notably osteoarthritis and rheumatoid arthritis (Academic Press Dictionary of Science Technology; Academic Press; 1st edition, January 15, 1992). The compounds of Formula I are also useful, alone or in combination, to treat or prevent arthritic conditions, such as Behcet's disease; bursitis and tendinitis; CPPD deposition disease; carpal tunnel syndrome; Ehlers-Danlos syndrome; fibromyalgia; gout; infectious arthritis; inflammatory bowel disease; juvenile arthritis; lupus erythematosus; lyme disease; marfan syndrome; myositis; osteoarthritis; osteogenesis imperfecta; osteonecrosis; polyarteritis; polymyalgia rheumatica; psoriatic

arthritis; Raynaud's phenomenon; reflex sympathetic dystrophy syndrome; Reiter's syndrome; rheumatoid arthritis; scleroderma; and Sjogren's syndrome. An embodiment of the invention encompasses the treatment or prevention of an arthrtic condition which comprises administering a therapeutically effective amount of a Compound of Formula I. A subembodiment is the treatment or prevention of osteoarthritis, which comprises administering a therapeutically effective amount of a Compound of Formula I. See: Cutolo M, Seriolo B, Villaggio B, Pizzorni C, Craviotto C, Sulli A. Ann. N.Y. Acad. Sci. 2002 Jun;966:131-42; Cutolo, M. Rheum Dis Clin North Am 2000 Nov;26(4):881-95; Bijlsma JW, Van den Brink HR. Am J Reprod Immunol 1992 Oct-Dec;28(3-4):231-4; Jansson L, Holmdahl R.; Arthritis Rheum 2001 Sep;44(9):2168-75; and Purdie DW. Br Med Bull 2000; 56(3):809-23. Also, see Merck Manual, 17th edition, pp. 449-451.

When used in combination to treat arthritic conditions, the Compounds of Formula I can be used with any of the drugs diclosed herein as useful for combination therapy, or can be used with drugs known to treat or prevent arrthritic conditions, such as corticosteroids, cytoxic drugs (or other disease modifying or remission inducing drugs), gold treatment, methotrexate, NSAIDs, and COX-2 inhibitors.

In another embodiment, the compounds of the present invention can be used to treat conditions in a female individual which are caused by androgen deficiency or which can be ameliorated by androgen replacement, including, but not limited to, osteoporosis, osteopenia, aging skin, glucocorticoid-induced osteoporosis, postmenopausal symptoms, periodontal disease, HIV-wasting, cancer cachexia, obesity, anemias, such as for example, aplastic anemia, muscular dystrophies, Alzheimer's disease, premature ovarian failure, cognitive decline, sexual dysfunction, depression, inflammatory arthritis and joint repair, atherosclerosis, and autoimmune disease, alone or in combination with other active agents. Treatment is effected by administration of a therapeutically effective amount of a compound of structural formula I to a female individual in need of such treatment.

The compounds of formula I are also useful in the enhancement of muscle tone in mammals, such as for example, humans. The compounds of structural formula I can also be employed as adjuncts to traditional androgen depletion therapy in the treatment of prostate cancer to restore bone, minimize bone loss, and maintain bone mineral density. In this manner, they can be employed together with traditional androgen deprivation therapy, including GnRH agonists/antagonists, such as those disclosed in P. Limonta, et al., "LHRH analogues as anticancer agents: pituitary and extrapituitary sites of action," Exp. Opin. Invest. Drugs, 10: 709-720 (2001); H.J. Stricker, "Luteinizing hormone-releasing hormone antagonists," Urology, 58 (Suppl. 2A): 24-27 (2001); R.P. Millar, et al., "Progress towards the development of non-peptide orally-active GnRH antagonists," British Medical Bulletin, 56: 761-772 (2000); and A.V. Schally et al., "Rational use of agonists and antagonists of LH-RH in the treatment of

hormone-sensitive neoplasms and gynecologic conditions," Advanced Drug Delivery Reviews, 28: 157-169 (1997). The compounds of structural formula I can be used in combination with antiandrogens, such as flutamide, 2-hydroxyflutamide (the active metabolite of flutamide), nilutamide, and bicalutamide (Casodex™) in the treatment of prostate cancer.

Further, the compounds of the present invention can also be employed in the treatment of pancreatic cancer, either for their androgen antagonist properties or as an adjunct to an antiandrogen, such as flutamide, 2-hydroxyflutamide (the active metabolite of flutamide), nilutamide, and bicalutamide (Casodex™).

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

Compounds of structural formula I can minimize the negative effects on lipid metabolism. Therefore, considering their tissue selective androgen agonistic properties, the compounds of this invention exhibit advantages over existing approaches for hormone replacement therapy in hypogonadic (androgen deficient) male individuals.

Additionally, compounds of the present invention can increase the number of blood cells, such as red blood cells and platelets, and can be used for treatment of hematopoietic disorders, such as aplastic anemia.

In one embodiment of the invention, therapeutically effective amounts of the compound of Formula I, are administered to the mammal, to treat or improve disorders selected from enhancement of weakened muscle tone, osteoporosis, osteopenia, glucocorticoid-induced osteoporosis, periodontal disease, bone fracture, bone damage following bone reconstructive surgery, sarcopenia, frailty, aging skin, male hypogonadism, postmenopausal symptoms in women, atherosclerosis, hypercholesterolemia, hyperlipidemia, obesity, aplastic anemia and other hematopoietic disorders, pancreatic cancer, inflammatory arthritis and joint repair, HIV-wasting, prostate cancer, benign prostatic hyperplasia (BPH), cancer cachexia, Alzheimer's disease, muscular dystrophies, cognitive decline, sexual dysfunction, sleep apnea, depression, premature ovarian failure, and autoimmune disease.

In another embodiment, therapeutically effective amounts of the compound can be used to treat or improve a disorder selected from weakened muscle tone, osteoporosis, osteopenia, glucocorticoid-induced osteoporosis, periodontal disease, bone fracture, bone damage following bone reconstructive surgery, sarcopenia, Alzheimer's disease, and frailty.

In another embodiment, the compound in accordance with the invention can be used to treat or improve a disorder such as male hypogonadism, postmenopausal symptoms in women,

atherosclerosis, hypercholesterolemia, hyperlipidemia, obesity, aplastic anemia and other hematopoietic disorders, pancreatic cancer, inflammatory arthritis and joint repair, HIV-wasting, prostate cancer, benign prostatic hyperplasia (BPH), cancer cachexia, muscular dystrophies, cognitive decline, sexual dysfunction, sleep apnea, depression, premature ovarian failure, and autoimmune disease.

The compounds of the present invention can be admisistered in their enantiomerically pure form. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

As used herein, a compound of the present invention which functions as an "agonist" of the androgen receptor can bind to the androgen receptor and initiate a physiological or a pharmacological response characteristic of that receptor. The term "tissue-selective androgen receptor modulator" refers to an androgen receptor ligand that mimics the action of a natural ligand in some tissues but not in others. A "partial agonist" is an agonist which is unable to induce maximal activation of the receptor population, regardless of the amount of compound applied. A "full agonist" induces full activation of the androgen receptor population at a given concentration. A compound of the present invention which functions as an "antagonist" of the androgen receptor can bind to the androgen receptor and block or inhibit the androgen-associated responses normally induced by a natural androgen receptor ligand.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Non-limiting representive salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In one variant of the invention, the salts are chosen from the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Non-limiting examples of salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts can be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Representative acids which can be employed include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic,

formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. In one variant, the acids are selected from citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It would also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not be deleterious to the recipient thereof.

The terms "administration of a compound" and "administering a compound" should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

By the term "modulating a function mediated by the androgen receptor in a tissue selective manner" it is meant modulating a function mediated by the androgen receptor selectively (or discriminately) in anabolic (bone and/or muscular) tissue (bone and muscular) in the absence of such modulation at androgenic (reproductive) tissue, such as the prostate, testis, seminal vesicles, ovary, uterus, and other sex accessory tissues. In one embodiment, the function of the androgen receptor in anabolic tissue is activated whereas the function of the androgen receptor in androgenic tissue is blocked or suppressed. In another embodiment, the function of the androgen receptor in anabolic tissue is blocked or suppressed whereas the function of the androgen receptor in androgenic tissue is activated.

The administration of a compound of structural formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the patient in need of such treatment or prophylaxis. The need for a prophylactic

administration according to the methods of the present invention is determined via the use of well-known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration, other drugs and treatments which the patient can concomitantly require, and other factors in the physician's judgment.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention can alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

Generally, the daily dosage of a compound of structural formula I can be varied over a wide range from about 0.01 to about 1000 mg per adult human per day. For example, dosages range from about 0.1 to about 200 mg/day. For oral administration, the compositions can be provided in the form of tablets containing from about 0.01 to about 1000 mg, such as for example, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 3.0, 5.0, 6.0, 10.0, 15.0, 25.0, 50.0, 75, 100, 125, 150, 175, 180, 200, 225, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the mammal to be treated.

The dose can be administered in a single daily dose or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, based on the properties of the individual compound selected for administration, the dose can be administered less frequently, e.g., weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

When administered via intranasal routes, transdermal routes, by rectal or vaginal suppositories, or through an intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Formulations of the tissue-selective androgen receptor modulator employed in the present method for medical use comprise a compound of structural formula I together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be

pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not being deleterious to the recipient subject of the formulation.

The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of structural formula I together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, rectal, intravaginal, topical or parenteral (including subcutaneous, intramuscular and intravenous administration). In one embodiment, the formulations are those suitable for oral administration.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, solutions, ointments, gels, lotions, dusting powders, and the like. The topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.005% to about 5% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle. Transdermal skin patches useful for administering the compounds of the present invention include those well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The formulations can be presented in a unit dosage form and can be prepared by any of the methods known in the art of pharmacy. All methods include the step of bringing the active compound in association with a carrier, which constitutes one or more ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound in association with a liquid carrier, a waxy solid carrier or a finely divided solid carrier, and then, if needed, shaping the product into the desired dosage form.

Formulations of the present invention suitable for oral administration can be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, or an emulsion.

A tablet can be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active compound in a free flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents, disintegrating agents or coloring agents. Molded tablets can be made by molding in a suitable machine a mixture of the active compound, preferably in powdered form, with a suitable carrier. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes and the like.

Non-limiting representative lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral liquid forms, such as syrups or suspensions in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl cellulose and the like, can be made by adding the active compound to the solution or suspension. Additional dispersing agents which can be employed include glycerin and the like.

Formulations for vaginal or rectal administration can be presented as a suppository with a conventional carrier, i.e., a base that is nontoxic and nonirritating to mucous membranes, compatible with a compound of structural formula I, and is stable in storage and does not bind or interfere with the release of the compound of structural formula I. Suitable bases include: cocoa butter (theobroma oil), polyethylene glycols (such as carbowax and polyglycols), glycol-surfactant combinations, polyoxyl 40 stearate, polyoxyethylene sorbitan fatty acid esters (such as Tween, Myrj, and Arlacel), glycerinated gelatin, and hydrogenated vegetable oils. When glycerinated gelatin suppositories are used, a preservative such as methylparaben or propylparaben can be employed.

Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention can also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamidephenol, or polyethylene-oxide polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Formulations suitable for parenteral administration include formulations that comprise a sterile aqueous preparation of the active compound which can be isotonic with the blood of the recipient. Such formulations suitably comprise a solution or suspension of a compound that is isotonic with the blood of the recipient subject. Such formulations can contain distilled water, 5% dextrose in distilled water or saline and the active compound. Often it is useful to employ a pharmaceutically and pharmacologically acceptable acid addition salt of the active compound that has appropriate solubility for the solvents employed. Useful formulations also comprise concentrated solutions or solids comprising the active compound which on dilution with an appropriate solvent give a solution suitable for parenteral administration.

The compounds of the present invention can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

The pharmaceutical composition and method of the present invention can further comprise other therapeutically active compounds usually applied in the treatment of the above mentioned conditions, including osteoporosis, periodontal disease, bone fracture, bone damage following bone reconstructive surgery, sarcopenia, frailty, aging skin, male hypogonadism, post-menopausal symptoms in women, atherosclerosis, hypercholesterolemia, hyperlipidemia, hematopoietic disorders, such as for example, aplastic anemia, pancreatic cancer, Alzheimer's disease, inflammatory arthritis, and joint repair.

For the treatment and prevention of osteoporosis, the compounds of the present invention can be administered in combination with a bone-strengthening agent selected from antiresorptive agents, osteoanabolic agents, and other agents beneficial for the skeleton through mechanisms which are not precisely defined, such as calcium supplements, flavonoids, and vitamin D analogs. The conditions of periodontal disease, bone fracture, and bone damage following bone reconstructive surgery can also benefit from these combined treatments. For example, the compounds of the instant invention can be effectively administered in combination with effective amounts of other agents such as estrogens, bisphosphonates, SERMs, cathepsin K inhibitors, $\alpha v\beta 3$ integrin receptor antagonists, vacuolar ATPase inhibitors, the polypeptide osteoprotegerin, antagonists of VEGF, thiazolidinediones, calcitonin, protein kinase inhibitors, parathyroid hormone (PTH) and analogs, calcium receptor antagonists, growth hormone secretagogues, growth hormone releasing hormone, insulin-like growth factor, bone morphogenetic protein (BMP), inhibitors of BMP antagonism, prostaglandin derivatives, fibroblast growth factors, vitamin D and derivatives thereof, vitamin K and derivatives thereof, soy isoflavones,

calcium salts, and fluoride salts. The conditions of periodontal disease, bone fracture, and bone damage following bone reconstructive surgery can also benefit from these combined treatments.

In one embodiment of the present invention, a compound of the instant invention can be effectively administered in combination with an effective amount of at least one bone-strengthening agent chosen from estrogen, and estrogen derivatives, alone or in combination with progestin or progestin derivatives; bisphosphonates; antiestrogens or selective estrogen receptor modulators; αvβ3 integrin receptor antagonists; cathepsin K inhibitors; osteoclast vacuolar ATPase inhibitors; calcitonin; and osteoprotegerin.

In the treatment of osteoporosis, the activity of the compounds of the present invention are distinct from that of the anti-resorptive agents: estrogens, bisphosphonates, SERMs, calcitonin, cathepsin K inhibitors, vacuolar ATPase inhibitors, agents interfering with the RANK/RANKL/Osteoprotegerin pathway, p38 inhibitors or any other inhibitors of osteoclast generation or osteoclast activation. Rather than inhibiting bone resorption, the compounds of structural formula I aid in the stimulation of bone formation, acting, for example, on cortical bone, which is responsible for a significant part of bone strength. The thickening of cortical bone substantially contributes to a reduction in fracture risk, especially fractures of the hip. The combination of the tissue-selective androgen receptor modulators of structural formula I with anti-resorptive agents such as for example estrogen, bisphosphonates, antiestrogens, SERMs, calcitonin, αvβ3 integrin receptor antagonists, HMG-CoA reductase inhibitors, vacuolar ATPase inhibitors, and cathepsin K inhibitors is particularly useful due to the complementory effect of the bone anabolic and antiresorptive actions.

Bone antiresportive agents are those agents which are known in the art to inhibit the resorption of bone and include, for example, estrogen and estrogen derivatives which include steroidal compounds having estrogenic activity such as, for example, 17β-estradiol, estrone, conjugated estrogen (PREMARIN®), equine estrogen, 17β-ethynyl estradiol, and the like. The estrogen or estrogen derivative can be employed alone or in combination with a progestin or progestin derivative. Nonlimiting examples of progestin derivatives are norethindrone and medroxy-progesterone acetate.

Bisphosphonates are also bone anti-resorptive agents. Non-limiting examples of bisphosphonate compounds which can also be employed in combination with a compound of structural formula I of the present invention include:

(a) alendronate (also known as alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, alendronate sodium, alendronate monosodium trihydrate or 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate. Alendronate is described in U.S. Patents 4,922,007, to Kieczykowski et al., issued May 1, 1990; 5,019,651, to Kieczykowski, issued May 28, 1991; 5,510,517, to Dauer et al., issued

April 23, 1996; 5,648,491, to Dauer et al., issued July 15, 1997, all of which are incorporated by reference herein in their entirety;

(b) [(cycloheptylamino)-methylene]-bis-phosphonate (incadronate), which is described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety;

(c) (dichloromethylene)-bis-phosphonic acid (clodronic acid) and the disodium salt (clodronate), which are described in Belgium Patent 672,205 (1966) and *J. Org. Chem 32*, 4111 (1967), both of which are incorporated by reference herein in their entirety;

(d) [1-hydroxy-3-(1-pyrrolidinyl)-propylidene]-bis-phosphonate (EB-1053);

(e) (1-hydroxyethylidene)-bis-phosphonate (etidronate);

(f) [1-hydroxy-3-(methylpentylamino)propylidene]-bis-phosphonate (ibandronate), which is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety;

(g) (6-amino-1-hydroxyhexylidene)-bis-phosphonate (neridronate);

(h) [3-(dimethylamino)-1-hydroxypropylidene]-bis-phosphonate (olpadronate);

(i) (3-amino-1-hydroxypropylidene)-bis-phosphonate (pamidronate);

(j) [2-(2-pyridinyl)ethylidene]-bis-phosphonate (piridronate), which is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety;

(k) [1-hydroxy-2-(3-pyridinyl)-ethylidene]-bis-phosphonate (risedronate);

(l) {[(4-chlorophenyl)thio]methylene}-bis-phosphonate (tiludronate), which is described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety;

(m) [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]-bis-phosphonate (zoledronate); and

(n) [1-hydroxy-2-imidazopyridin-(1,2-a)-3-ylethylidene]-bis-phosphonate (minodronate).

In one embodiment of the methods and compositions of the present invention, the bisphosphonate is chosen from alendronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zoledronate, pharmaceutically acceptable salts of these bisphosphonates, and mixtures thereof. In one variant, the bisphosphonate is selected from alendronate, risedronate, zoledronate, ibandronate, tiludronate, and clodronate. In a subclass of this class, the bisphosphonate is alendronate, pharmaceutically acceptable salts and hydrates thereof, and mixtures thereof. A particular pharmaceutically acceptable salt of alendronate is alendronate monosodium. Pharmaceutically acceptable hydrates of alendronate monosodium include the monohydrate and the trihydrate. A particular pharmaceutically acceptable salt

of risedronate is risedronate monosodium. Pharmaceutically acceptable hydrates of risedronate monosodium include the hemi-pentahydrate.

Still further, antiestrogenic compounds such as raloxifene (see, e.g., U.S. Patent No. 5,393,763), clomiphene, zuclomiphene, enclomiphene, nafoxidene, CI-680, CI-628, CN-55,945-27, Mer-25, U-11,555A, U-100A, and salts thereof, and the like (see, e.g., U.S. Patent Nos. 4,729,999 and 4,894,373) can be employed in combination with a compound of structural formula I in the methods and compositions of the present invention. These agents are also known as SERMs, or selective estrogen receptor modulators, agents known in the art to prevent bone loss by inhibiting bone resorption via pathways believed to be similar to those of estrogens.

SERMs can be used in combination with the compounds of the Formula I to beneficially treat bone disorders including osteoporosis. Such agents include, for example, tamoxifen, raloxifene, lasofoxifene, toremifene, azorxifene, EM-800, EM-652, TSE 424, clomiphene, droloxifene, idoxifene, and levormeloxifene [Goldstein, et al., "A pharmacological review of selective estrogen receptor modulators," Human Reproduction Update, 6: 212-224 (2000), and Lufkin, et al., "The role of selective estrogen receptor modulators in the prevention and treatment of osteoporosis," Rheumatic Disease Clinics of North America, 27: 163-185 (2001)]. SERMs are also discussed in "Targeting the Estrogen Receptor with SERMs," Ann. Rep. Med. Chem. 36: 149-158 (2001).

$\alpha v\beta 3$ Integrin receptor antagonists suppress bone resorption and can be employed in combination with the tissue selective androgen receptor modulators of structural formula I for the treatment of bone disorders including osteoporosis. Peptidyl as well as peptidomimetic antagonists of the $\alpha v\beta 3$ integrin receptor have been described both in the scientific and patent literature. For example, reference is made to W.J. Hoekstra and B.L. Poulter, Curr. Med. Chem. 5: 195-204 (1998) and references cited therein; WO 95/32710; WO 95/37655; WO 97/01540; WO 97/37655; WO 98/08840; WO 98/18460; WO 98/18461; WO 98/25892; WO 98/31359; WO 98/30542; WO 99/15506; WO 99/15507; WO 00/03973; EP 853084; EP 854140; EP 854145; US Patent Nos. 5,204,350; 5,217,994; 5,639,754; 5,741,796; 5,780,426; 5,929,120; 5,952,341; 6,017,925; and 6,048,861.

Evidence of the ability of $\alpha v\beta 3$ integrin receptor antagonists to prevent bone resorption in vitro and in vivo has been presented (see V.W. Engleman et al., "A Peptidomimetic Antagonist of the $\alpha v\beta 3$ Integrin Inhibits Bone Resorption In Vitro and Prevents Osteoporosis In Vivo," J. Clin. Invest. 99: 2284-2292 (1997); S.B. Rodan et al., "A High Affinity Non-Peptide $\alpha v\beta 3$ Ligand Inhibits Osteoclast Activity In Vitro and In Vivo," J. Bone Miner. Res. 11: S289 (1996); J.F. Gourvest et al., "Prevention of OVX-Induced Bone Loss With a Non-peptidic Ligand of the $\alpha v\beta 3$ Vitronectin Receptor," Bone 23: S612 (1998); M.W. Lark et al., "An Orally Active Vitronectin Receptor $\alpha v\beta 3$ Antagonist Prevents Bone

Resorption In Vitro and In Vivo in the Ovariectomized Rat," Bone 23: S219 (1998)). Other αvβ3 antagonists are described in R.M. Keenan et al., "Discovery of Potent Nonpeptide Vitronectin Receptor (αvβ3) Antagonists," J. Med. Chem. 40: 2289-2292 (1997); R.M. Keenan et al., "Benzimidazole Derivatives As Arginine Mimetics in 1,4-Benzodiazepine Nonpeptide Vitronectin Receptor (αvβ3) Antagonists," Bioorg. Med. Chem. Lett. 8: 3165-3170 (1998); and R.M. Keenan et al., "Discovery of an Imidazopyridine-Containing 1,4-Benzodiazepine Nonpeptide Vitronectin Receptor (αvβ3) Antagonist With Efficacy in a Restenosis Model," Bioorg. Med. Chem. Lett. 8: 3171-3176 (1998).

Still other benzazepine, benzodiazepine and benzocycloheptene αvβ3 integrin receptor antagonists are described in the following patent publications: WO 96/00574, WO 96/00730, WO 96/06087, WO 96/26190, WO 97/24119, WO 97/24122, WO 97/24124, WO 98/14192, WO 98/15278, WO 99/05107, WO 99/06049, WO 99/15170, WO 99/15178, WO 99/15506, and U.S. Patent No. 6,159,964, and WO 97/34865. αvβ3 integrin receptor antagonists having dibenzocycloheptene, dibenzocycloheptane and dibenzoxazepine scaffolds have been described in WO 97/01540, WO 98/30542, WO 99/11626, WO 99/15508, WO 00/33838, U.S. Patent Nos. 6,008,213, and 6,069,158.

Other osteoclast integrin receptor antagonists incorporating backbone conformational ring constraints have been described in the patent literature. Published patent applications or issued patents disclosing antagonists having a phenyl constraint include WO 98/00395, WO 99/32457, WO 99/37621, WO 99/44994, WO 99/45927,WO 99/52872, WO 99/52879, WO 99/52896, WO 00/06169, EP 0 820,988, EP 0 820,991, U.S. Patent Nos. 5,741,796; 5,773,644; 5,773,646; 5,843,906; 5,852,210; 5,929,120; 5,952,381; 6,028,223; and 6,040,311. Published patent applications or issued patents disclosing antagonists having a monocyclic ring constraint include WO 99/26945, WO 99/30709, WO 99/30713, WO 99/31099, WO 99/59992, WO 00/00486, WO 00/09503, EP 0 796,855, EP 0 928,790, EP 0 928,793, U.S. Patent Nos. 5,710,159; 5,723,480; 5,981,546; 6,017,926; and 6,066,648. Published patent applications or issued patents disclosing antagonists having a bicyclic ring constraint include WO 98/23608, WO 98/35949, WO 99/33798, EP 0 853,084, U.S. Patent Nos. 5,760,028; 5,919,792; and 5,925,655.

Reference is also made to the following reviews for additional scientific and patent literature that concern alpha v integrin antagonists: M. E. Duggan, et al., "Ligands to the integrin receptor $\alpha_v\beta_3$, Exp. Opin. Ther. Patents, 10: 1367-1383 (2000); M. Gowen, et al., "Emerging therapies for osteoporosis," Emerging Drugs, 5: 1-43 (2000); J.S. Kerr, et al., "Small molecule α_v integrin antagonists: novel anticancer agents," Exp. Opin. Invest. Drugs, 9: 1271-1291 (2000); and W.H. Miller, et al., "Identification and in vivo efficacy of small-molecule antagonists of integrin $\alpha_v\beta_3$ (the vitronectin receptor)," Drug Discovery Today, 5: 397-408 (2000).

Cathepsin K, formerly known as cathepsin O2, is a cysteine protease and is described in PCT International Application Publication No. WO 96/13523, published May 9, 1996; U.S. Patent No. 5,501,969, issued March 3, 1996; and U.S. Patent No. 5,736,357, issued April 7, 1998, all of which are incorporated by reference herein in their entirety. Cysteine proteases, specifically cathepsins, are linked to a number of disease conditions, such as tumor metastasis, inflammation, arthritis, and bone remodeling. At acidic pH's, cathepsins can degrade type-I collagen. Cathepsin protease inhibitors can inhibit osteoclastic bone resorption by inhibiting the degradation of collagen fibers and are thus useful in the treatment of bone resorption diseases, such as osteoporosis. Non-limiting examples of cathespin K inhibitors can be found in PCT International Publications assigned to Merck Frost Canada and Axix Pharmaceuticals: WO 01/49288, published July 7, 2001, and WO 01/77073, published October 18, 2001.

Members of the class of HMG-CoA reductase inhibitors, known as the "statins," have been found to trigger the growth of new bone, replacing bone mass lost as a result of osteoporosis (see The Wall Street Journal, Friday, December 3, 1999, page B1). Therefore, the statins hold promise for the treatment of bone resorption. Examples of HMG-CoA reductase inhibitors include statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784); dihydroxy open-acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the sodium salt thereof (see US Patent No. 4,346,227); fluvastatin, particularly the sodium salt thereof (see US Patent No. 5,354,772); atorvastatin, particularly the calcium salt thereof (see US Patent No. 5,273,995); cerivastatin, particularly the sodium salt thereof (see US Patent No. 5,177,080), rosuvastatin, also known as ZD-4522 (see US Patent No. 5,260,440) and pitavastatin, also referred to as NK-104, itavastatin, or nisvastatin (see PCT international application publication number WO 97/23200).

Osteoclast vacuolar ATPase inhibitors, also called proton pump inhibitors, can also be employed together with the tissue selective androgen receptor modulators of structural formula I. The proton ATPase which is found on the apical membrane of the osteoclast has been reported to play a significant role in the bone resorption process. Therefore, this proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases [see C. Farina et al., "Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents," DDT, 4: 163-172 (1999)].

The angiogenic factor VEGF has been shown to stimulate the bone-resorbing activity of isolated mature rabbit osteoclasts via binding to its receptors on osteoclasts [see M. Nakagawa et al., "Vascular endothelial growth factor (VEGF) directly enhances osteoclastic bone resorption and survival

of mature osteoclasts," FEBS Letters, 473: 161-164 (2000)]. Therefore, the development of antagonists of VEGF binding to osteoclast receptors, such as KDR/Flk-1 and Flt-1, can provide yet a further approach to the treatment or prevention of bone resorption.

Activators of the peroxisome proliferator-activated receptor-α (PPARα), such as the thiazolidinediones (TZD's), inhibit osteoclast-like cell formation and bone resorption *in vitro*. Results reported by R. Okazaki et al. in Endocrinology, 140: 5060-5065 (1999) point to a local mechanism on bone marrow cells as well as a systemic one on glucose metabolism. Nonlimiting examples of PPARα, activators include the glitazones, such as troglitazone, pioglitazone, rosiglitazone, and BRL 49653.

Calcitonin can also be employed together with the tissue selective androgen receptor modulator of structural formula I. Calcitonin is preferentially employed as salmon nasal spray (Azra et al., Calcitonin. 1996. In: J. P. Bilezikian, et al., Ed., Principles of Bone Biology, San Diego: Academic Press; and Silverman, "Calcitonin," Rheumatic Disease Clinics of North America, 27: 187-196, 2001)

Protein kinase inhibitors can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Kinase inhibitors include those disclosed in WO 01/17562 and are in one embodiment selected from inhibitors of p38. Non-limiting examples of p38 inhibitors useful in the present invention include SB 203580 [Badger et al., "Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock, and immune function," J. Pharmacol. Exp. Ther., 279: 1453-1461 (1996)].

Osteoanabolic agents are those agents that are known to build bone by increasing the production of the bone protein matrix. Such osteoanabolic agents include, for example, the various forms of parathyroid hormone (PTH) such as naturally occurring PTH (1-84), PTH (1-34), analogs thereof, native or with substitutions and particularly parathyroid hormone subcutaneous injection. PTH has been found to increase the activity of osteoblasts, the cells that form bone, thereby promoting the synthesis of new bone (Modern Drug Discovery, Vol. 3, No. 8, 2000). An injectable recombinant form of human PTH, Forteo (teriparatide), has received regulatory approval in the U.S. for the treatment of osteoporosis. Thus, PTH and fragments thereof, such as hPTH(1-34), can prove to be efficacious in the treatment of osteoporosis alone or in combination with other agents, such as the tissue selective androgen receptor modulators of the present invention.

Also useful in combination with the SARMs of the present invention are calcium receptor antagonists which induce the secretion of PTH as described by Gowen et al., in "Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats," J. Clin. Invest. 105: 1595-604 (2000).

Additional osteoanabolic agents include growth hormone secretagogues, growth hormone, growth hormone releasing hormone and the like can be employed with the compounds according to structural formula I for the treatment of osteoporosis. Representative growth hormone secretagogues are disclosed in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; U.S. Patent No. 5,494,919; U.S. Patent No. 5,494,920; U.S. Patent No. 5,492,916; U.S. Patent No. 5,536,716; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; PCT Patent Pub. No. WO 95/34311; PCT Patent Pub. No. WO 96/02530; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28: 177-186 (1993); Bioorg. Med. Chem. Lett., 4: 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA, 92: 7001-7005 (1995).

Insulin-like growth factor (IGF) can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Insulin-like growth factors can be selected from Insulin-like Growth Factor I, alone or in combination with IGF binding protein 3 and IGF II [See Johannson and Rosen, "The IGFs as potential therapy for metabolic bone diseases," 1996, In: Bilezikian, et al., Ed., Principles of Bone Biology, San Diego: Academic Press; and Ghiron et al., "Effects of recombinant insulin-like growth factor-I and growth hormone on bone turnover in elderly women," J. Bone Miner. Res. 10: 1844-1852 (1995)].

Bone morphogenetic protein (BMP) can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Bone morphogenetic protein includes BMP 2, 3, 5, 6, 7, as well as related molecules TGF beta and GDF 5 [Rosen et al., "Bone morphogenetic proteins," 1996. In: J. P. Bilezikian, et al., Ed., Principles of Bone Biology, San Diego: Academic Press; and Wang EA, "Bone morphogenetic proteins (BMPs): therapeutic potential in healing bony defects," Trends Biotechnol., 11: 379-383 (1993)].

Inhibitors of BMP antagonism can also be employed together with the tissue selective androgen receptor modulators of structural formula I. In one embodiment, BMP antagonist inhibitors are chosen from inhibitors of the BMP antagonists SOST, noggin, chordin, gremlin, and dan [Massague and Chen, "Controlling TGF-beta signaling," Genes Dev., 14: 627-644, 2000;

Aspenberg et al., "The bone morphogenetic proteins antagonist Noggin inhibits membranous ossification," J. Bone Miner. Res. 16: 497-500, 2001; Brunkow et al., "Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein," Am. J. Hum. Genet. 68: 577-89 (2001)].

The tissue-selective androgen receptor modulators of the present invention can also be combined with the polypeptide osteoprotegerin for the treatment of conditions associated with bone loss, such as osteoporosis. The osteoprotegerin can be selected from mammalian osteoprotegerin and human osteoprotegerin. The polypeptide osteoprotegerin, a member of the tumor necrosis factor receptor super-family, is useful to treat bone diseases characterized by increased bone loss, such as osteoporosis. Reference is made to U.S. Patent No. 6,288,032, which is incorporated by reference herein in its entirety.

Prostaglandin derivatives can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Non-limiting representatives of prostaglandin derivatives are selected from agonists of prostaglandin receptors EP1, EP2, EP4, FP, IP and derivatives thereof [Pilbeam et al., "Prostaglandins and bone metabolism," 1996. In: Bilezikian, et al. Ed. Principles of Bone Biology, San Diego: Academic Press; Weinreb et al., "Expression of the prostaglandin E(2) (PGE(2)) receptor subtype EP(4) and its regulation by PGE(2) in osteoblastic cell lines and adult rat bone tissue," Bone, 28: 275-281 (2001)].

Fibroblast growth factors can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Fibroblast growth factors include aFGF, bFGF and related peptides with FGF activity [Hurley Florkiewicz, "Fibroblast growth factor and vascular endothelial growth factor families," 1996. In: J. P. Bilezikian, et al., Ed. Principles of Bone Biology, San Diego: Academic Press].

In addition to bone resorption inhibitors and osteoanabolic agents, there are also other agents known to be beneficial for the skeleton through mechanisms which are not precisely defined. These agents can also be favorably combined with the tissue selective androgen receptor modulators of structural formula I.

Vitamin D and vitamin D derivatives can also be employed together with the tissue selective androgen receptor modulator of structural formula I. Vitamin D and vitamin D derivatives include, for example, natural vitamin D, 25-OH-vitamin D_3, 1α,25$(OH)_2$ vitamin D_3, 1α-OH-vitamin D_3, 1α-OH-vitamin D_2, dihydrotachysterol, 26,27-F6-1α,25$(OH)_2$ vitamin D_3, 19-nor-1α,25$(OH)_2$ vitamin D_3, 22-oxacalcitriol, calcipotriol, 1α,25$(OH)_2$-16-ene-23-yne-vitamin D_3 (Ro 23-7553), EB1089, 20-epi-1α,25$(OH)_2$ vitamin D_3, KH1060, ED71, 1α,24(S)-$(OH)_2$ vitamin D_3, 1α,24(R)-$(OH)_2$

vitamin D_3 [See, Jones G., "Pharmacological mechanisms of therapeutics: vitamin D and analogs," 1996. In: J. P. Bilezikian, et al. Ed. Principles of Bone Biology, San Diego: Academic Press].

Vitamin K and vitamin K derivatives can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Vitamin K and vitamin K derivatives include menatetrenone (vitamin K2) [see Shiraki et al., "Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis," J. Bone Miner. Res., 15: 515-521 (2000)].

Soy isoflavones, including ipriflavone, can be employed together with the tissue selective androgen receptor modulators of structural formula I.

Fluoride salts, including sodium fluoride (NaF) and monosodium fluorophosphate (MFP), can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Dietary calcium supplements can also be employed together with the tissue selective androgen receptor modulators of structural formula I. Dietary calcium supplements include calcium carbonate, calcium citrate, and natural calcium salts (Heaney. Calcium. 1996. In: J. P. Bilezikian, et al., Ed., Principles of Bone Biology, San Diego: Academic Press).

Daily dosage ranges for bone resorption inhibitors, osteoanabolic agents and other agents which can be used to benefit the skeleton when used in combination with a compound of structural formula I are those which are known in the art. In such combinations, generally the daily dosage range for the tissue selective androgen receptor modulator of structural formula I ranges from about 0.01 to about 1000 mg per adult human per day, such as for example, from about 0.1 to about 200 mg/day. However, adjustments to decrease the dose of each agent can be made due to the increased efficacy of the combined agent.

In particular, when a bisphosphonate is employed, dosages from about 2.5 to about 100 mg/day (measured as the free bisphosphonic acid) are appropriate for treatment, such as for example ranging from 5 to 20 mg/day, or about 10 mg/day. Prophylactically, doses of about 2.5 to about 10 mg/day and especially about 5 mg/day should be employed. For reduction in side-effects, it can be desirable to administer the combination of a compound of structural formula I and the bisphosphonate once a week. For once weekly administration, doses ranging from about 15 mg to about 700 mg per week of bisphosphonate and from about 0.07 to about 7000 mg of a compound of structural formula I can be employed, either separately, or in a combined dosage form. A compound of structural formula I can be favorably administered in a controlled-release delivery device, particularly for once weekly administration.

For the treatment of atherosclerosis, hypercholesterolemia, and hyperlipidemia, the compounds of structural formula I can be effectively administered in combination with one or more

additional active agents. The additional active agent or agents can be chosen from lipid-altering compounds such as HMG-CoA reductase inhibitors, agents having other pharmaceutical activities, and agents that have both lipid-altering effects and other pharmaceutical activities. Non-limiting examples of HMG-CoA reductase inhibitors include statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin (see US Patent No. 4,342,767); simvastatin (see US Patent No. 4,444,784); dihydroxy open-acid simvastatin, particularly the ammonium or calcium salts thereof; pravastatin, particularly the sodium salt thereof (see US Patent No. 4,346,227); fluvastatin, particularly the sodium salt thereof (see US Patent No. 5,354,772); atorvastatin, particularly the calcium salt thereof (see US Patent No. 5,273,995); cerivastatin, particularly the sodium salt thereof (see US Patent No. 5,177,080), and nisvastatin, also referred to as NK-104 (see PCT international application publication number WO 97/23200).

Additional active agents which can be employed in combination with a compound of structural formula I include, but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and -2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; cholesterol absorption inhibitors, such as SCH-58235, also known as ezetimibe and 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone, which is described in U.S. Patent Nos. 5,767,115 and 5,846,966; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPARα), agonists, including the compounds commonly referred to as glitazones, for example troglitazone, pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidinediones as well as those PPARα, agonists outside the thiazolidinedione structural class; PPARα agonists, such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual α/γ agonists; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin converting enzyme inhibitors, such as enalapril and captopril; calcium channel blockers, such as nifedipine and diltiazem; endothelin antagonists; agents such as LXR ligands that enhance ABC1 gene expression; bisphosphonate compounds, such as alendronate sodium; and cyclooxygenase-2 inhibitors, such as rofecoxib and celecoxib, as well as other agents known to be useful in the treatment of these conditions.

Daily dosage ranges for HMG-CoA reductase inhibitors when used in combination with the compounds of structural formula I correspond to those which are known in the art. Similarly, daily dosage ranges for the HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and -2; microsomal triglyceride transfer protein (MTP) inhibitors; probucol; niacin; cholesterol absorption inhibitors including ezetimibe; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; platelet aggregation inhibitors, including glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPARγ) agonists; PPARα agonists; PPAR dual α/γ agonists; vitamin B_6; vitamin B_{12}; folic acid; anti-oxidant vitamins; beta-blockers; angiotensin II antagonists; angiotensin converting enzyme inhibitors; calcium channel blockers; endothelin antagonists; agents such as LXR ligands that enhance ABC1 gene expression; bisphosphonate compounds; and cyclooxygenase-2 inhibitors also correspond to those which are known in the art, although due to the combined action with the compounds of structural formula I, the dosage can be somewhat lower when administered in combination.

One embodiment of the invention is a method for effecting a bone turnover marker in a mammal comprising administering a therapeutically effective amount of a compound according to formula I. Non-limiting examples of bone turnover markers can be selected from urinary C-telopeptide degradation products of type I collagen (CTX), urinary N-telopeptide cross-links of type I collagen (NTX), osteocalcin (bone Gla protein), dual energy x-ray absorptionmetry (DXA), bone specific alkaline phosphatase (BSAP), quantitative ultrasound (QUS), and deoxypyridinoline (DPD) crosslinks.

In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating diseases caused by androgen deficiency or that can be ameliorated by addition of androgen.

<u>Abbreviations Used in the Description of the Preparation of the Compounds of the Present Invention:</u>

AcOH	Acetic acid
DHT	Dihydrotestosterone
DMAP	4-Dimethylaminopyridine
DMEM	Dulbecceo modified eagle media

DMSO	Dimethyl sulfoxide
DMF	N,N-Dimethylformamide
EA	Ethyl acetate
EDC	1-(3-Dimethylaminopropyl)3-ethylcarbodiimide HCl
EDTA	Ethylenediaminetetraacetic acid
EtOH	Ethanol
Et_3N	Triethylamine
FCS	Fetal calf serum
HEPES	(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	High-performance liquid chromatography
KHMDS	Potassium bistrimethylsilylamide
LCMS	Liquid chromotography/mass spectroscopy
LDA	Lithium diisopropylamide
LG	Leaving group
MeOH	Methanol
NBS	N-bromosuccinimide
n-Bu4NI	Tetra-n-butylammonium iodide
PMBCL	p-Methoxybenzyl chloride
p-TosCl	p-Toluenesulfonyl chloride
Rt or rt	Room temperature
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound in place of multiple substituents which are allowed under the definitions of Formula I defined previously.

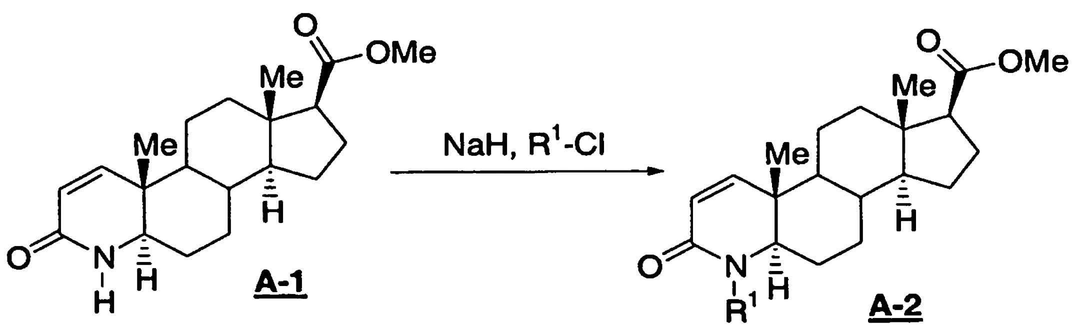
Schemes A-D provide general guidelines for making compounds of Formula I. Scheme A illustrates the addition of the R^1 substituent on the 4-azasteroidal backbone having an unsubstituted 2-

position carbon. Scheme B illustrates the addition of the R^1 and the X substituents on the 4-azasteroidal backbone at positions 4 and 2, respectively.

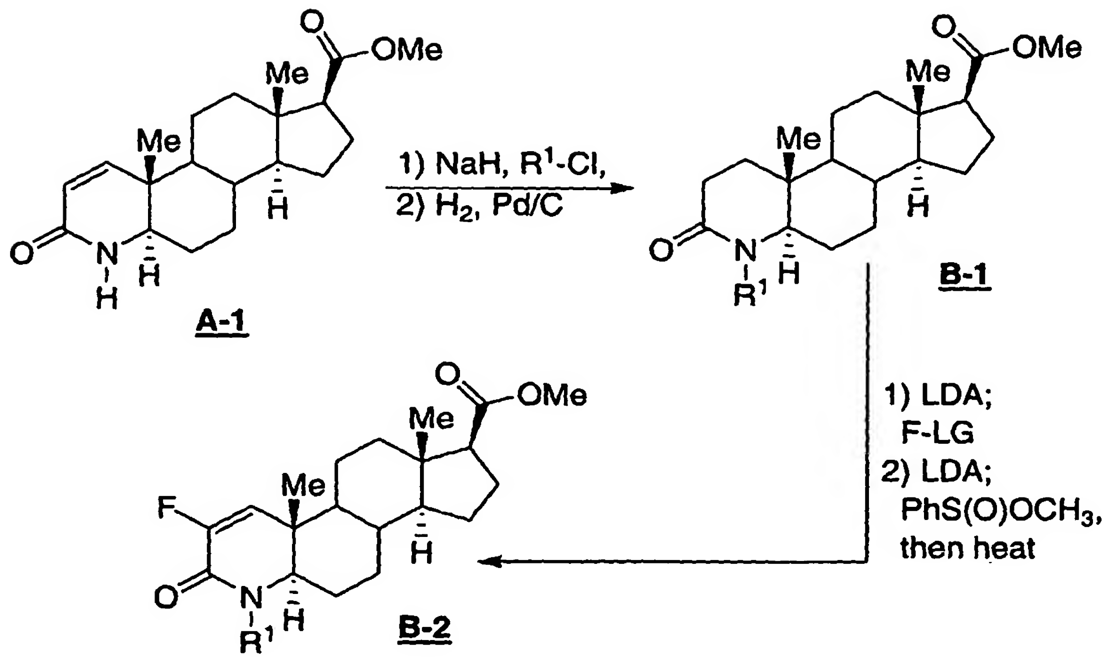
Scheme C illustrates the addition of the heterocyclic, benzimidazolyl and azabenzimidazolyl moieties at position 21 of the 4-azasteroidal backbone. Scheme D illustrates the placement of R^2 and R^3 substituents.

It should be noted that in Schemes B and D, the selection of the particular leaving group, LG, will of course depend upon the particular substituent class that is incorporated onto the core structure. Selection and application of leaving groups is a common practice in the synthetic organic chemical art and this information is readily known and accessible to one skilled in the art. See for example, Organic Synthesis, Smith, M, McGraw-Hill INC, 1994, New York. ISBN 0-07-048716-2.

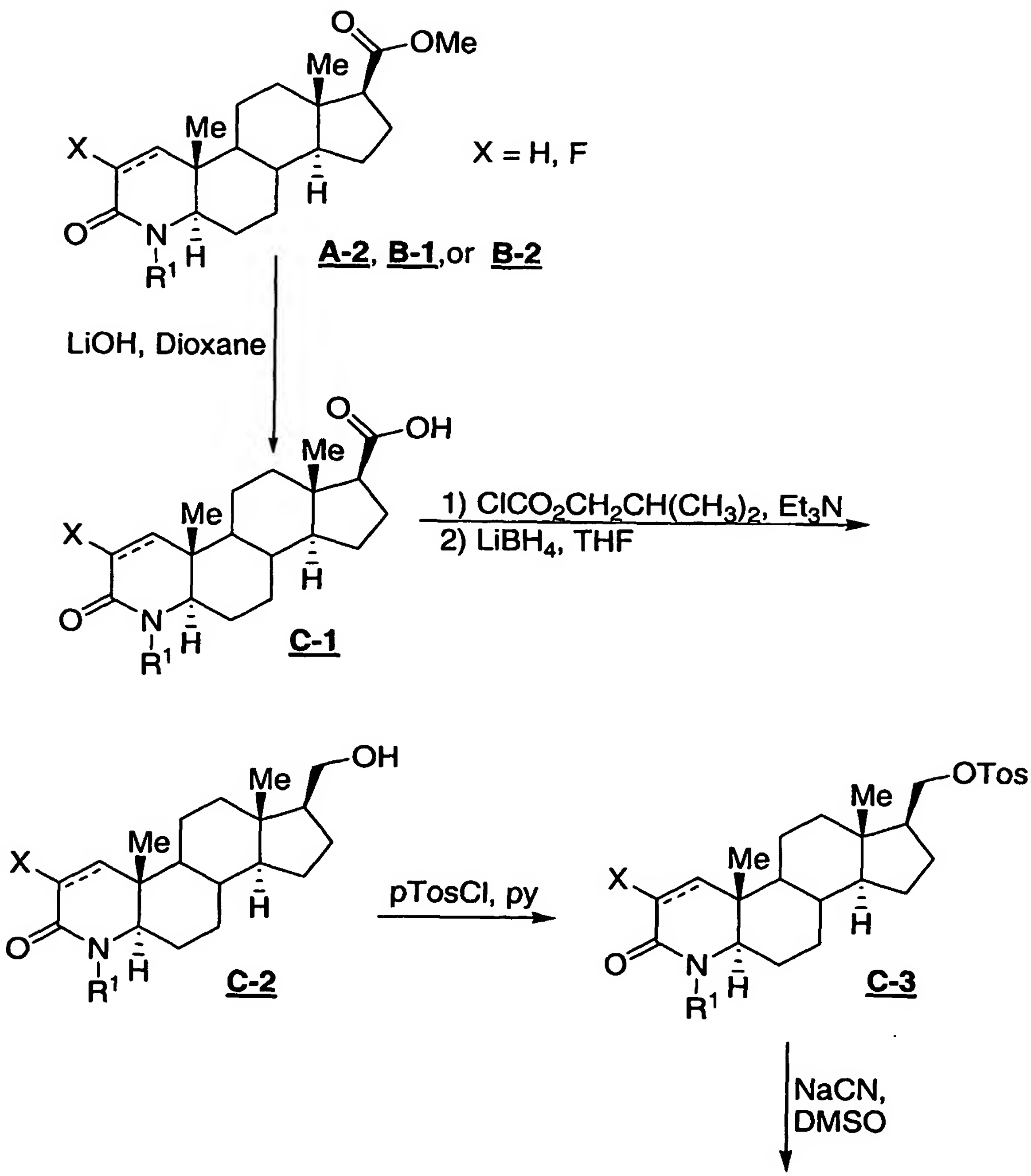
Scheme A



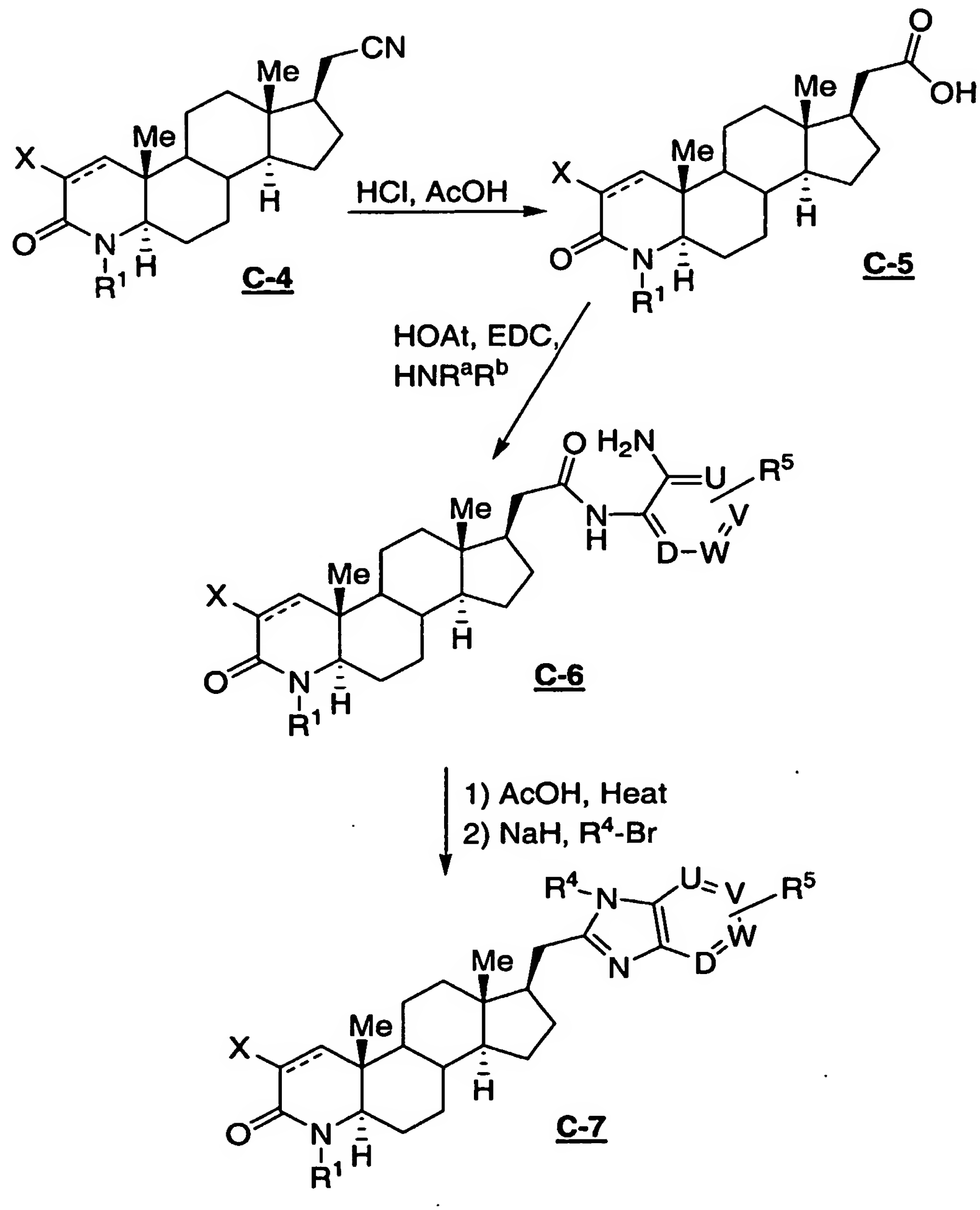
Scheme B


OMe
Me
Me
O
N
H
H
H
A-1
1) NaH, R1-Cl,
2) H2, Pd/C
B-1
R1
1) LDA;
F-LG
2) LDA;
PhS(O)OCH3,
then heat
F
B-2

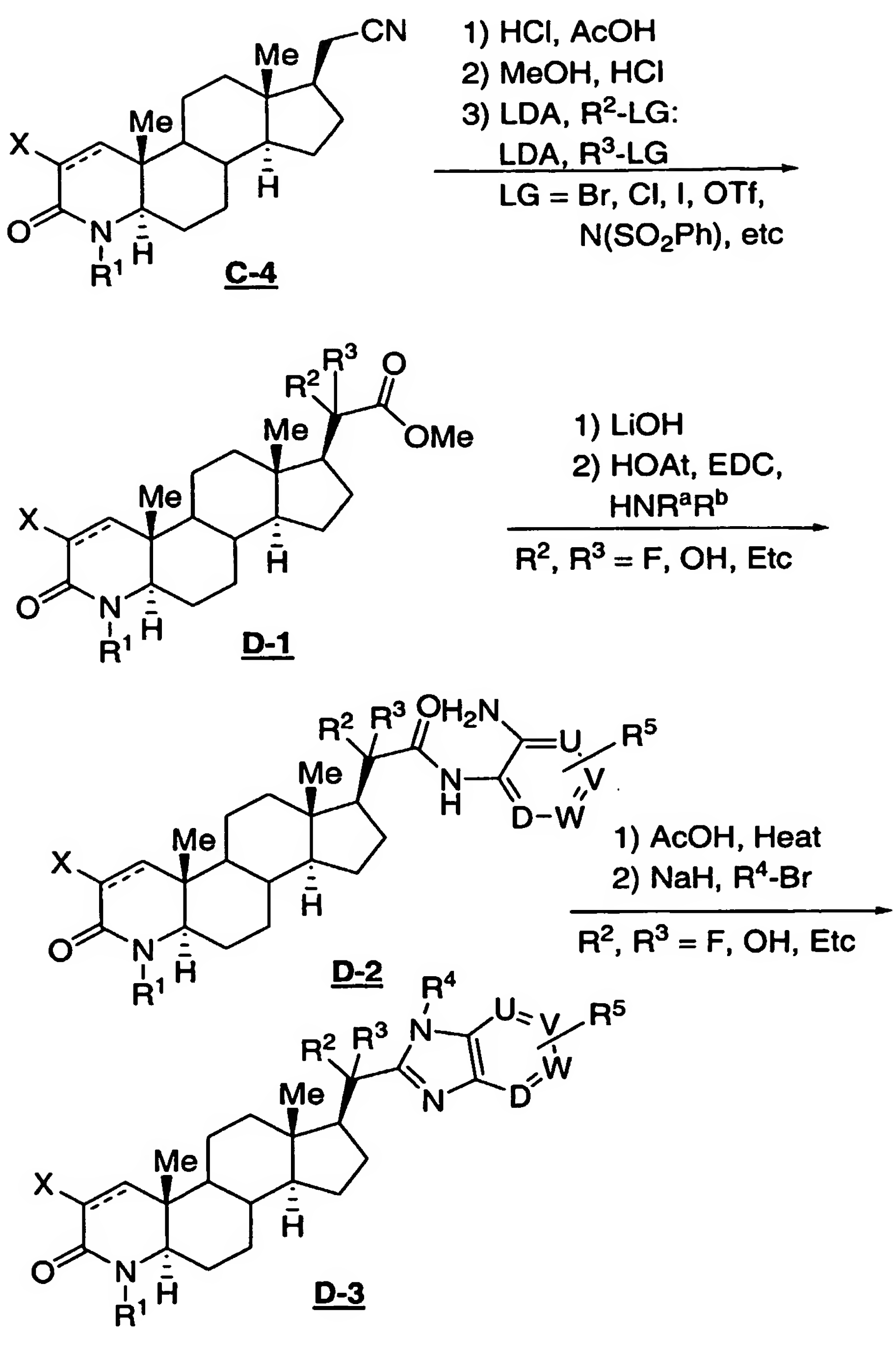
Scheme C


X = H, F
A-2, B-1, or B-2
LiOH, Dioxane
C-1
1) $ClCO_2CH_2CH(CH_3)_2$, Et_3N
2) $LiBH_4$, THF
C-2
pTosCl, py
C-3
NaCN,
DMSO

Scheme C con't



Scheme D


Me
CN
Me
X
O
N
R1
H
H
C-4
1) HCl, AcOH
2) MeOH, HCl
3) LDA, R2-LG:
LDA, R3-LG
LG = Br, Cl, I, OTf,
N(SO2Ph), etc
R3
R2
O
OMe
D-1
1) LiOH
2) HOAt, EDC,
HNRaRb
R2, R3 = F, OH, Etc
H2N
U
V
R5
D-W
D-2
1) AcOH, Heat
2) NaH, R4-Br
R2, R3 = F, OH, Etc
R4
D-3

EXAMPLES

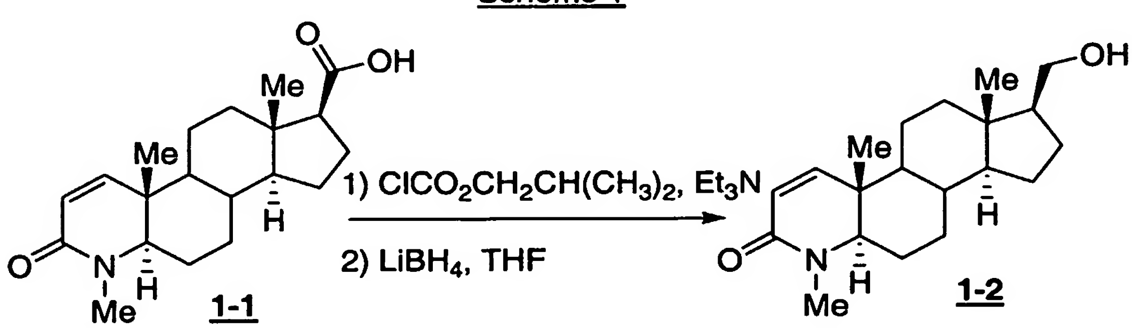
The compounds of the present invention can be prepared according to the procedures denoted in the following reaction Schemes and Examples or modifications thereof using readily available starting materials, reagents, and conventional procedures or variations thereof well-known to a practitioner of ordinary skill in the art of synthetic organic chemistry. Specific definitions of variables in the Schemes are given for illustrative purposes only and are not intended to limit the procedures described.

Preparation of the Compounds of the Invention

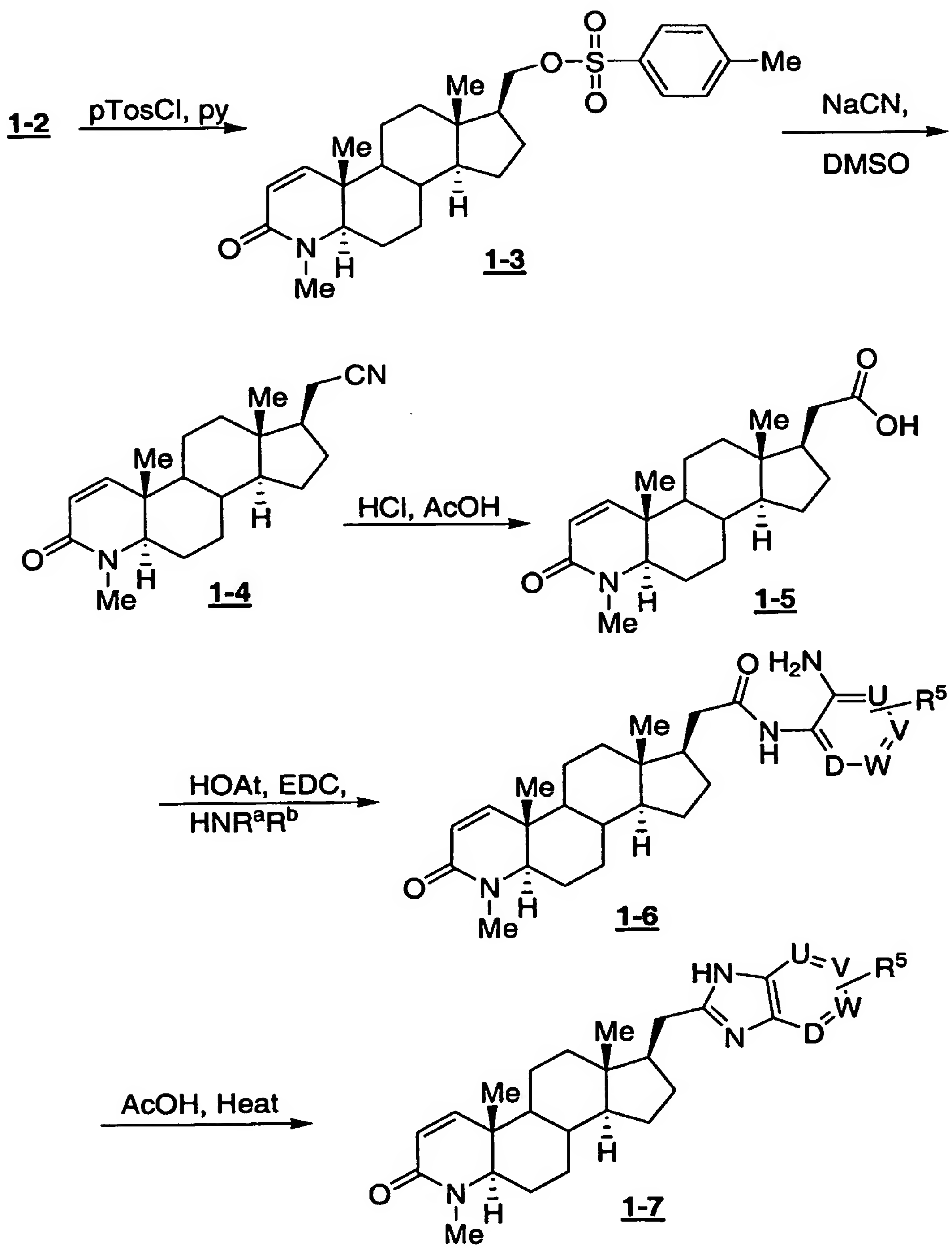
The compounds of the present invention can be prepared according to the procedures denoted in the following reaction Schemes and Examples or modifications thereof using readily available starting materials, reagents, and conventional procedures or variations thereof well-known to a practitioner of ordinary skill in the art of synthetic organic chemistry. Specific definitions of variables in the Schemes are given for illustrative purposes only and are not intended to limit the procedures described. The selective androgen receptor modulators (SARMs) of formula I were prepared as outlined in Schemes 1, 2, 3, 4, and 5.

The selective androgen receptor modulators (SARMs) of structural formula 1-7 were prepared as outlined in Scheme 1. The starting material was the 17β-carboxylic acid 1-1 which is disclosed in G.H. Rasmusson et al., J. Med. Chem., 29: 2298-2315 (1986) and R.L. Tolman, et al., J. Steroid Biochem. Mol. Biol., 60: 303-309 (1997), each incorporated by reference, herein.

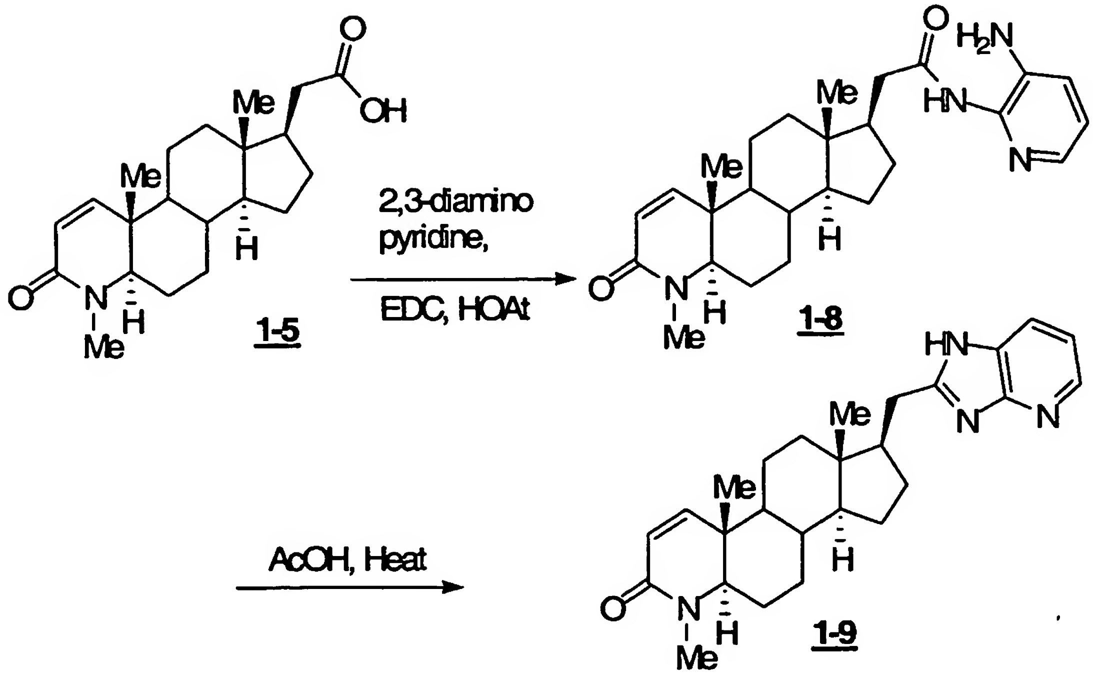
Scheme 1



Scheme 1 cont.



SCHEME 1 cont.



Example 1

Step A: 4-Methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carbinol (1-2)

To a solution of 1-1 (36.5 g, 110.12 mmol) in CH_2Cl_2:THF (1:1-500 mL) at 0°C was added Et_3N (20.0 mL, 143.2 mmol). *iso*-Butyl chloroformate (17.1 mL, 132.1 mmol) was added dropwise and after 30 mins the cooling bath was removed and the reaction was stirred for 2 hours. The reaction was then cooled to 0°C and a solution of 2 M $LiBH_4$ in THF (165.2 mL, 330.4 mmol) was added dropwise. The reaction was stirred at 0°C for 2 hours. The reaction was quenched by dropwise addition of a saturated solution of NH_4Cl (125 mL), diluted with CH_2Cl_2 (900 mL), washed with 1 N NaOH, brine, dried ($MgSO_4$) and then concentrated. The residue was azeotroped with toluene and dried under high vacuum for 18 hours before being used crude in next reaction (1-2). MS calculated M+H: 318, found 318.

Step B: 4-Methyl-3-oxo-4-aza-5α-androst-1-ene-17β-methyl tosylate (1-3)

To a solution of 1-2 (27.0 g crude, ca. 85.0 mmol) in CH_2Cl_2 (250 mL) at 0°C was added pyridine (50 mL) and *p*-TosCl (26.0 g, 136.1 mmol). After 30 minutes, the cooling bath was removed and the reaction was stirred for 15 hours. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (125 mL), diluted with CH_2Cl_2 (800 mL), washed with brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 1-3 as a white solid. MS calculated M+H: 472, found 472.

Step C: 4-Methyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetonitrile (1-4)

To a solution of 1-3 (43.0 g, 91 mmol) in DMSO (120 mL) at rt was added NaCN (17.9 g, 365mmol) slowly and the reaction was placed in an oil bath at 120°C and stirred for 2 hours. After cooling, the reaction was diluted with CH_2Cl_2 (1000 mL), washed with a saturated solution of $NaHCO_3$ (125 mL), brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 1-4 as a white solid. MS calculated M+H: 327, found 327.

Step D: 4-Methyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetic acid (1-5)

To a solution of 1-4 (28.7 g, 87.9 mmol) in AcOH (50 mL) at rt was added conc. HCl (50 mL) and the reaction was heated to 125°C and stirred for 14 hours. After cooling, the reaction was diluted with CH_2Cl_2 (800 mL), washed with cold water, a saturated solution of $NaHCO_3$, brine, dried ($MgSO_4$) and then concentrated. The residue was azeotroped with toluene to afford 1-5 as a yellow foam. MS calculated M+H: 346, found 346.

Step E: *N*-[2-(Amino)pyridin-3-yl]-4-methyl-3-oxo-4-aza-5α-androst-1-en-17β-acetamide (1-8)

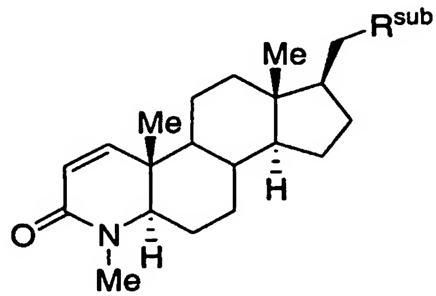
To a solution of 1-5 (3.50 g, 10.13 mmol) and HOAt (1.655 g, 12.157 mmol) in DMF (5.0 mL) was added EDC (2.331 g, 12.157 mmol) and the reaction was stirred at room temperature. After 15 minutes, 2,3-diaminopyridine (1.216 g, 11.144 mmol) was added and the reaction was heated to 60°C and stirred for 30 minutes. After cooling, the reaction was concentrated and azeotroped with toluene. The residue was purified by chromatography on silica gel (10:1 CH_2Cl_2:MeOH to 20:10:1:1 EtOAc:EtOH:H_2O:NH_3 aq.) to afford 1-8 as a white solid. MS calculated M+H: 437, found 437.

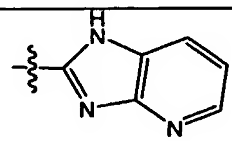
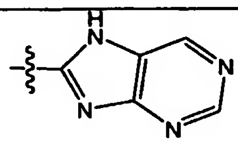
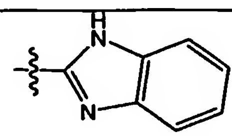
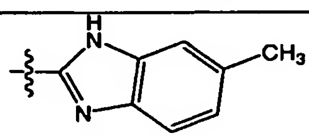
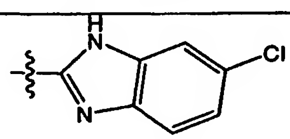
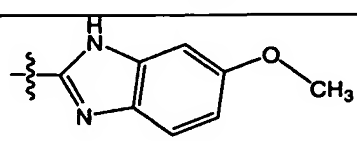
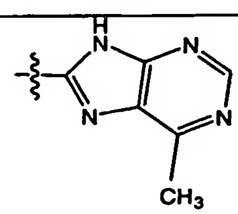
Step F: 17β-(1*H*-Imidazo[4,5-*b*]pyridin-2-yl)-4-methyl-4-aza-5α-androst-1-en-3-one (1-9)

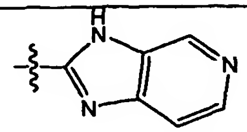
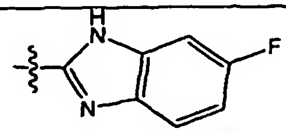
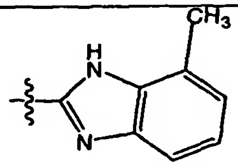
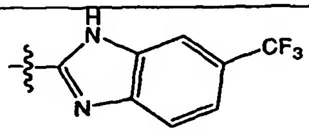
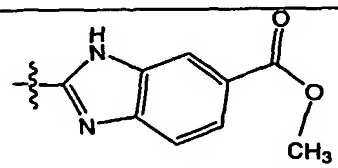
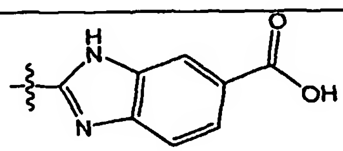
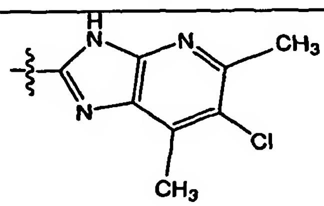
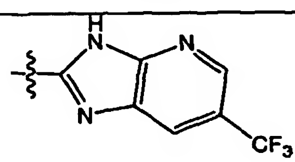
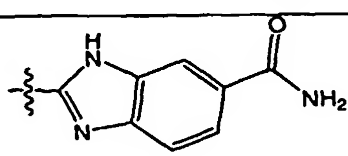
A solution of 1-8 (0.355 g, 0.813 mmol) in acetic acid (4.5 mL) was heated to 180 °C in the microwave and stirred for 45 minutes. After cooling, the reaction was concentrated and azeotroped with toluene. The residue was recrystallized from 20:1 CH_2Cl_2:MeOH, and the solid collected by filtration to afford 1-9 as a white solid. MS calculated M+H: 419, found 419.

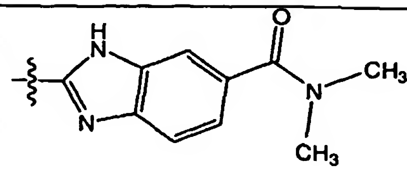
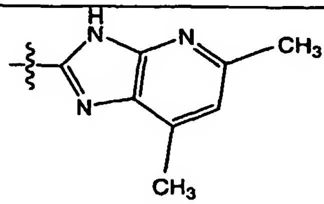
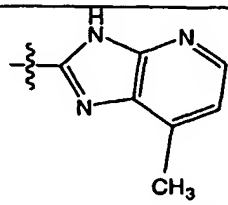
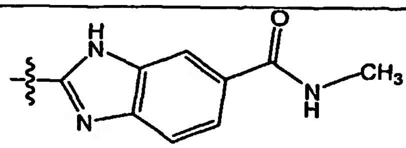
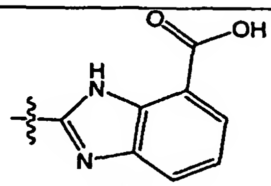
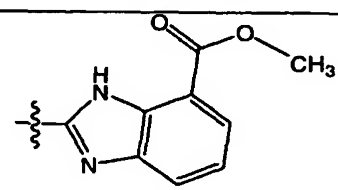
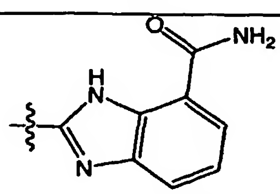
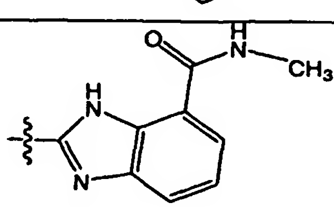
Examples 2-25 in Table 1 were prepared in a similar manner as Example 1, but using the appropriate amine to generate the carboxamide, followed by cyclization.

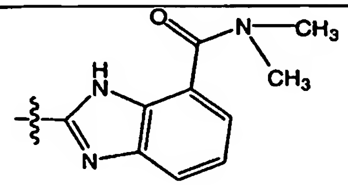
TABLE 1



Ex.	R^{sub}	Name	Mass spectrum Measured [M+H]
1		17β-(1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one	420.0
2		17β-(7*H*-purin-8-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one	419.0
3		17β-(1*H*-benzimidazol-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one	418.0
4		17β-[(5-methyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	432.0
5		17β-[(5-chloro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	452.0
6		17β-[(5-methoxy-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	448.0
7		17β-[(6-methyl-7*H*-purin-8-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	434.0

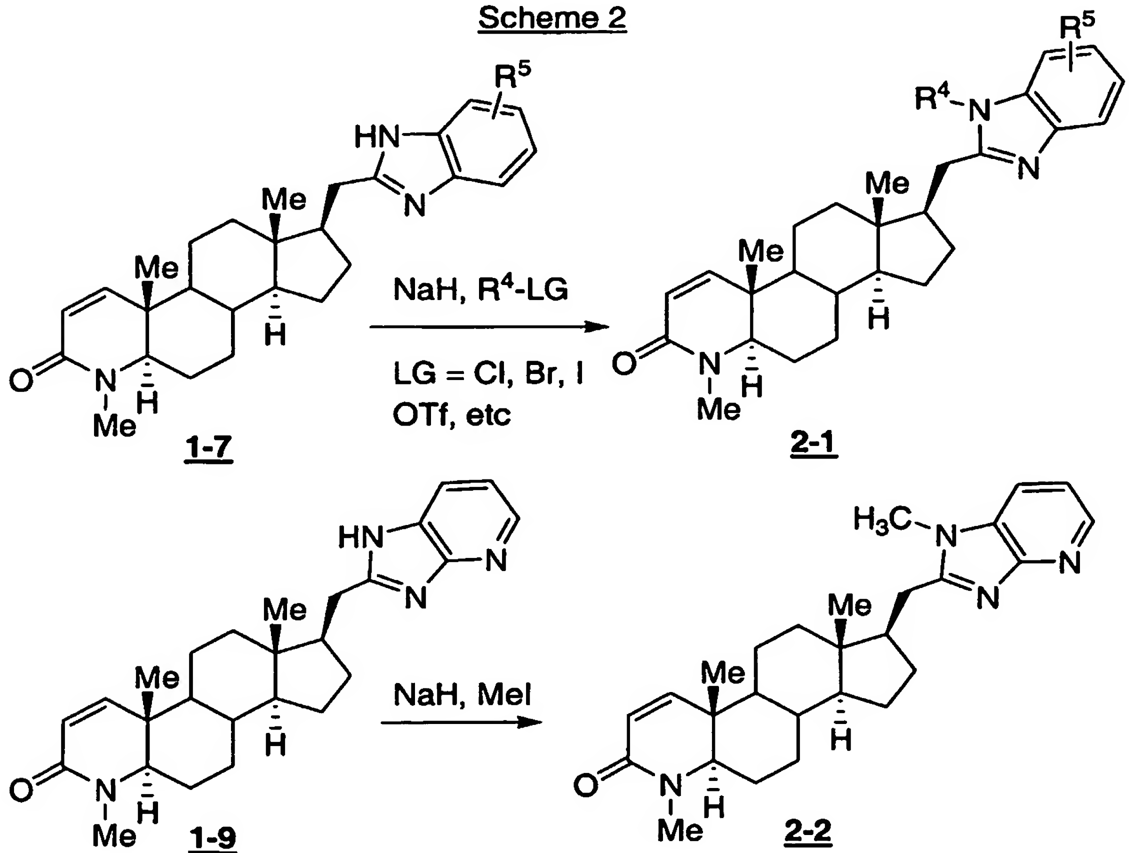
8		17β-(1*H*-imidazo[4,5-c]pyridin-2-ylmethyl)-4-methyl-4-aza-5α-androst-1-en-3-one	419.0
9		17β-[(5-fluoro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	436.0
10		17β-[(4-methyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	432.0
11		17β-[(5-trifluoromethyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	486.0
12		17β-[(5-methyl carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	476.0
13		17β-[(5- carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	462.0
14		17β-[(6-chloro-5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	481.0
15		17β-[(6-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	487.0
16		17β-[(5- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	461.1

17		17β-[(5-N, N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	489.1
18		17β-[(5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	447.1
19		17β-[(7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	433.0
20		17β-[(5-N-methyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	475.0
21		17β-[(6- carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	462.1
22		17β-[(6-methyl carboxyl-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	476.1
23		17β-[(6- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	461.1
24		17β-[(6-N-methyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	475.42

25		17β-[(6-N,N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one	489.44

The selective androgen receptor modulators (SARMs) of structural formula 2-1 were prepared as outlined in Scheme 2. The starting materials were prepared in Table 1.

Scheme 2



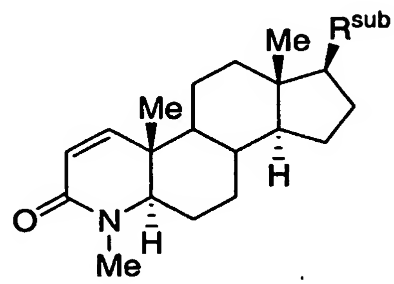
Example 26

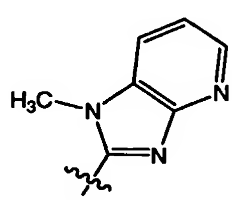
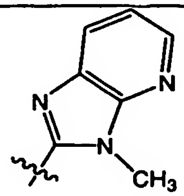
Step A: 17β-[(1-Methyl-imidazo[4,5-*b*]pyridin-2-yl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one (2-2)

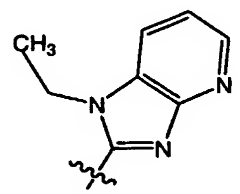
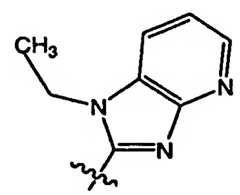
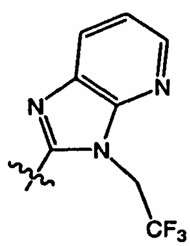
To a solution of 1-9 (0.05 g, 0.12 mmol) in DMF (0.5 mL) at rt, was added NaH (0.006 g, 0.24 mmol). After 20 mins, methyliodide (0.015 mL, 0.24 mmol) was added and the reaction was stirred at rt for 10 mins. The reaction was quenched with H_2O, diluted with CH_2Cl_2, and washed with brine. The organic layer was dried, filtered and concentrated. The residue was purified by flash chromatography (0-10% MeOH in CH_2Cl_2) to afford 2-2 as a white solid, as well as the N-methyl regioisomer (Table 2). MS calculated M+H: 433, found 433.

Examples 27-30 in Table 2 were prepared in a similar manner as Example 26, but using the appropriate alkylating agent.

TABLE 2

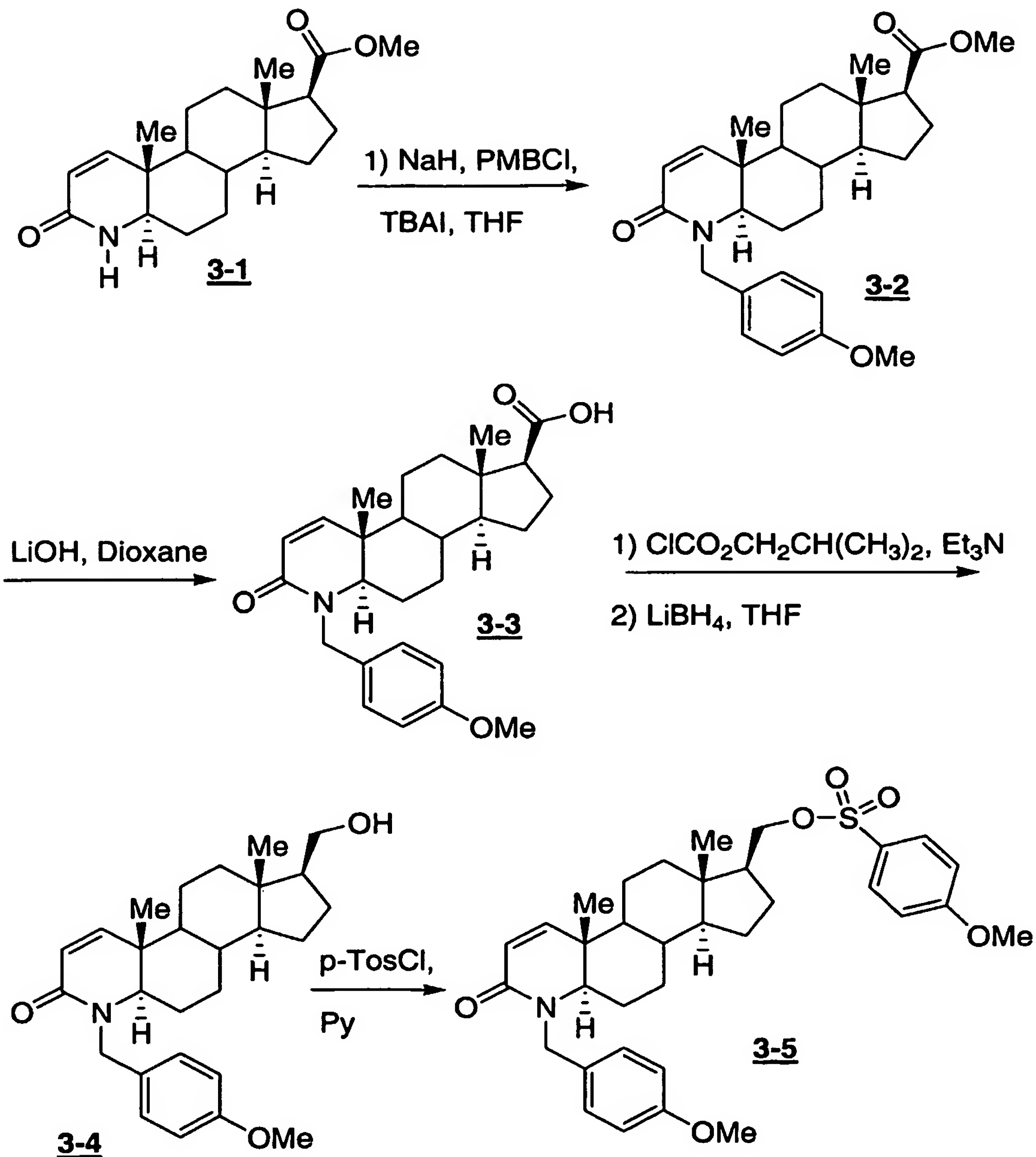


Ex.	R^sub	Name	Mass spectrum Measured [M+H]
26		17β-[(1-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one	433.1
27		17β-[(3-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one	433.1

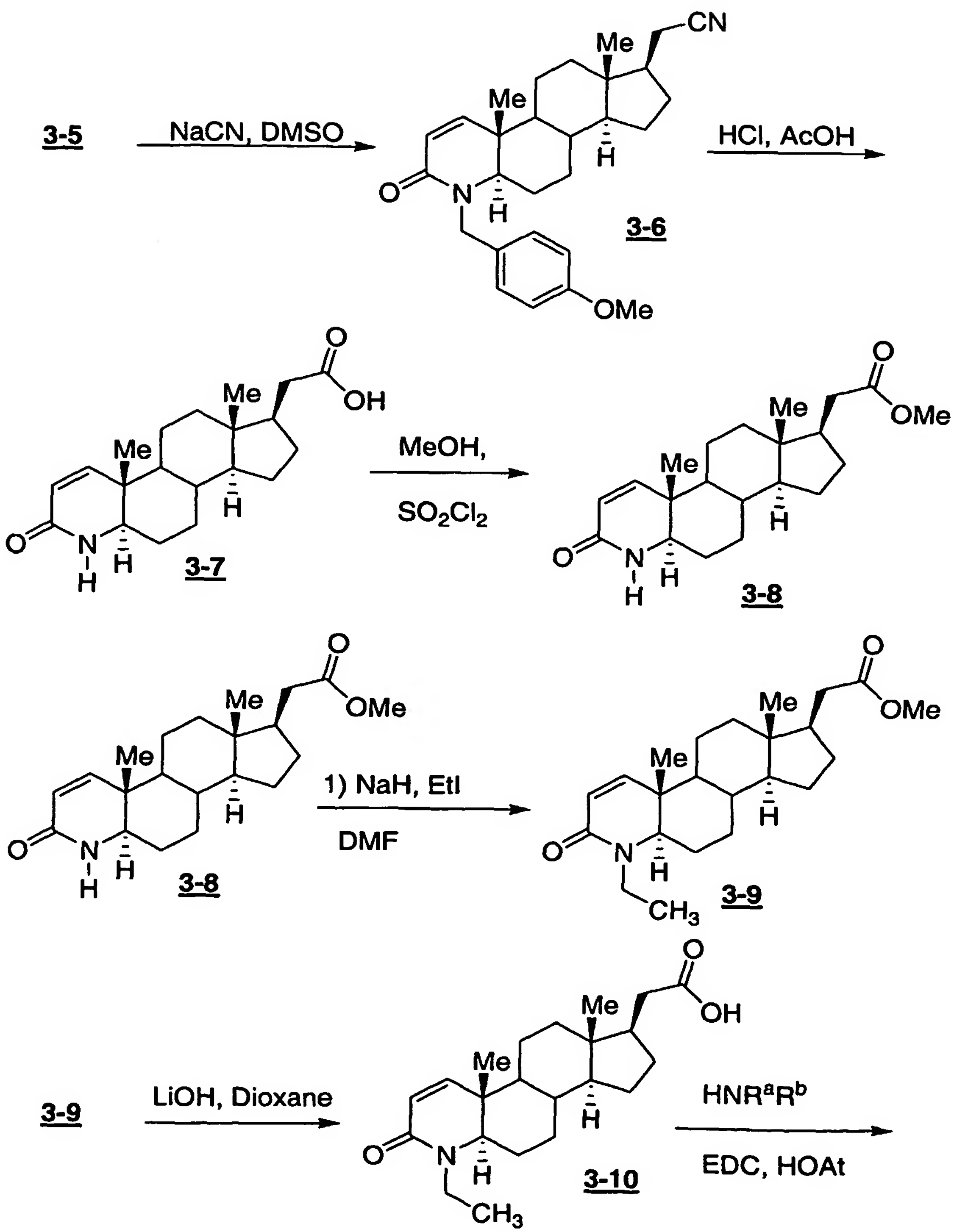
28		17β-[(1-ethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one	447.1
29		17β-[(1-ethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one	447.1
30		17β-[(3-trifluoroethyl-1H-imidazo[4,5-*b*]pyridin-2-yl)methyl)]-4-methyl-4-aza-5α-androst-1-en-3-one	501.1

The selective androgen receptor modulators (SARMs) of structural formula 3-12 were prepared as outlined in Scheme 3. The starting material was the methyl 17β-carboxylate 3-1 which is disclosed in G.H. Rasmusson et al., J. Med. Chem., 29: 2298-2315 (1986).

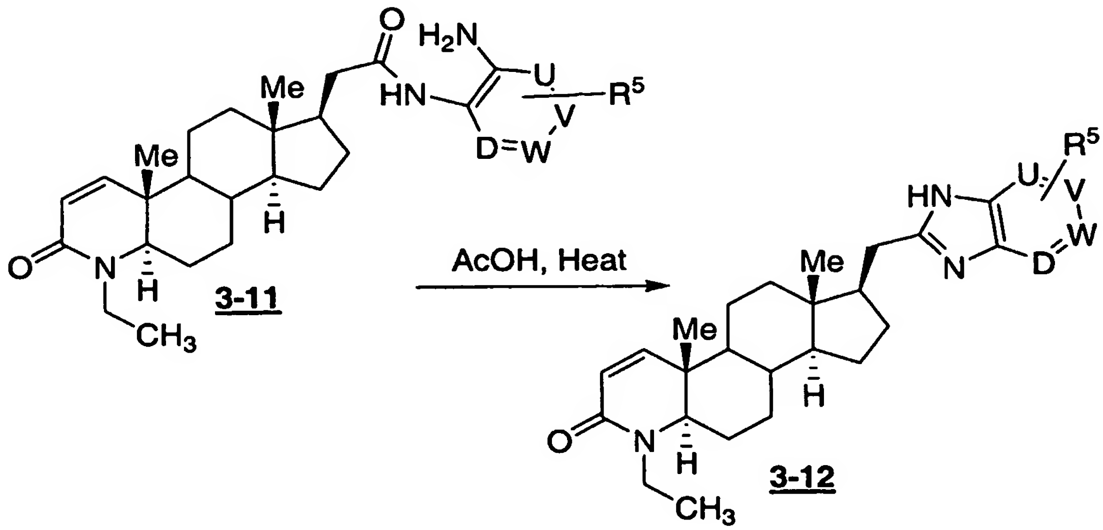
Scheme 3

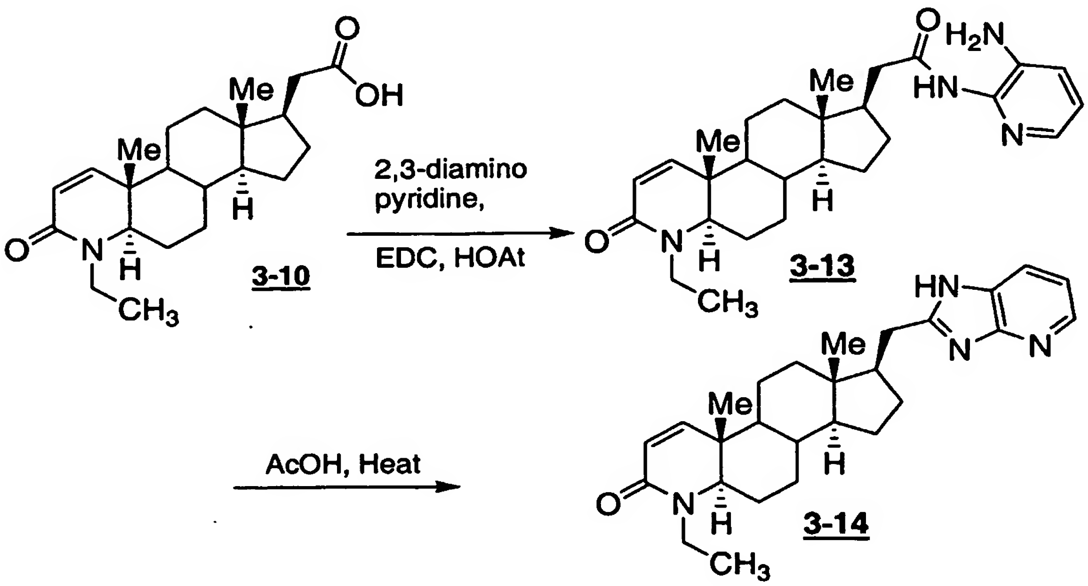

OMe
Me
Me
O
N
H
H
H
1) NaH, PMBCl,
TBAI, THF
3-1
3-2
OMe
LiOH, Dioxane
OH
3-3
1) ClCO2CH2CH(CH3)2, Et3N
2) LiBH4, THF
p-TosCl,
Py
O
S
3-4
3-5

Scheme 3 con't



Scheme 3 con't





Example 31

Step A: Methyl 4-*p*-methoxybenzyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate (3-2)

To a solution of 3-1 (10.0 g, 30.2 mmol) in THF (300 mL) at rt was added NaH (2.2 g, 45.3 mmol, 60% dispersion in mineral oil) and the resulting mixture was stirred for 30 mins. *p*-Methoxybenzyl chloride (6.4 mL, 45.3 mmol) and *n*-Bu_4NI (ca. 0.5 g) were added and the reaction was

heated to reflux and stirred for 4 hours. The reaction was then cooled to room temperature and the reaction was quenched by the dropwise addition of 1N HCl. The mixture was concentrated and the precipitate was collected and washed with H_2O and hexanes. The yellow solid 3-2 was dried under high vacuum for 18 hours. MS calculated M+H: 452, found 452.

Step B: 4-*p*-Methoxybenzyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid (3-3)

To a solution of 3-2 (13.6 g, 30.1 mmol) in dioxane (200 mL) at room temperature was added $LiOH{\cdot}H_2O$ (2.5 g, 60.2 mmol) and the reaction was heated to reflux and stirred for 4 hours. The reaction was cooled to room temperature and then concentrated. The residue was diluted with a 1 N solution of HCl and the precipitate was collected and washed with H_2O and hexanes to afford 3-3 as a white solid. MS calculated M+H: 438, found 438.

Step C: 4- *p*-Methoxybenzyl-3-oxo-4-aza-5α-androst-1-ene-17β-carbinol (3-4)

To a solution of 3-3 (13.1 g, 29.4 mmol) in CH_2Cl_2:THF (1:1-300 mL) at 0°C was added Et_3N (5.4 mL, 39.0 mmol). *iso*-Butyl chloroformate (4.7 mL, 36.0 mmol) was added dropwise and after 30 minutes the cooling bath was removed and the reaction was stirred for 2 hours. The reaction was then cooled to 0°C and a solution of 2 M $LiBH_4$ in THF (43.5 mL, 87.0 mmol) was added dropwise. The reaction was stirred at 0°C for 2 hours. The reaction was quenched by dropwise addition of a saturated solution of NH_4Cl (125 mL), diluted with CH_2Cl_2 (900mL), washed with 1 N NaOH, brine, dried ($MgSO_4$) and then concentrated. The residue was dissolved in a small amount of CH_2Cl_2 and triturated with Et_2O. The solid was filtered and washed with hexanes to afford 3-4 as a white solid. MS calculated M+H: 424, found 424.

Step D: 4-*p*-Methoxybenzyl-3-oxo-4-aza-5α-androst-1-ene-17β-methyl tosylate (3-5)

To a solution of 3-4 (45.0 g, 106.2 mmol) in CH_2Cl_2 (500 mL) at 0°C was added pyridine (100 mL) and *p*-TosCl (32.6 g, 170 mmol). After 30 minutes, the cooling bath was removed and the reaction was stirred for 15 hours. LCMS shows that the reaction is complete. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (125 mL), diluted with CH_2Cl_2 (800 mL), washed with brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 3-5 as a white waxy solid. MS calculated M+H: 578, found 578.

Step E: 4-*p*-Methoxybenzyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetonitrile (3-6)

To a solution of 3-3 (20.0 g, 34.6 mmol) in DMSO (120 mL) at room temperature was added NaCN (4.2 g, 86.5mmol) and the reaction was placed in an oil bath at 95°C and stirred for 2 hours. After cooling, the reaction was diluted with CH_2Cl_2 (800 mL), washed with a saturated solution of $NaHCO_3$ (125 mL), brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 3-6 as a white solid. MS calculated M+H: 327, found 327.

Step F: 3-Oxo-4-aza-5α-androst-1-ene-17β-acetic acid (3-7)

To a solution of 3-6 (7.8 g, 18.0 mmol) in AcOH (50 mL) at rt was added conc. HCl (50 mL) and the reaction was heated to 125°C and stirred for 14 hours. After cooling, the reaction was diluted with CH_2Cl_2 (800 mL), washed with cold water, a saturated solution of $NaHCO_3$, brine, dried ($MgSO_4$) and then concentrated. The residue was azeotroped with toluene to afford 3-7 as a yellow foam. MS calculated M+H: 332, found 332.

Step G: 17β-Methyl-3-Oxo-4-aza-5α-androst-1-ene-acetic ester (3-8)

To a solution of 3-7 (2.5 g, 7.55 mmol) in MeOH (100 mL) at rt was added thionylchloride (1.5 mL) and the reaction was heated to 80°C and stirred for 4 hours. After cooling, the reaction was diluted with CH_2Cl_2 (800 mL), washed with cold water, a saturated solution of $NaHCO_3$, brine, dried ($MgSO_4$) and then concentrated. . The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 3-8 as a white solid.
MS calculated M+H: 346, found 346.

Step H: Methyl 4-ethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate (3-9)

To a solution of 3-8 (2.12 g, 6.14 mmol) in DMF (20 mL) at 0 °C was added NaH (0.368 g, 9.20 mmol, 60% dispersion in mineral oil) and the resulting mixture was stirred for 15 mins. Iodoethane (0.73 mL, 9.20 mmol) was added and the reaction was stirred at rt for 2 hours. The reaction was then heated to 40 °C and stirred for 30 mins. The reaction was then cooled to room temperature, quenched H_2O, diluted with CH_2Cl_2 (800 mL), washed with cold water, a saturated solution of $NaHCO_3$, brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (25-100% EtOAc in hexanes) to afford 3-9 as a white solid. MS calculated M+H: 375, found 375.

Step I: 4-Ethyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid (3-10)

To a solution of 3-9 (1.50 g, 4.02 mmol) in MeOH:CH_2Cl_2 (8:1, 9.0 mL) at room temperature was added 5 N NaOH (12.0 mL) and the reaction was heated to 40°C and stirred for 20 mins. The reaction was cooled to room temperature and then concentrated. The residue was diluted with a 1 N solution of HCl and the precipitate was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and then concentrated to afford 3-10 as a white solid. MS calculated M+H: 360, found 360.

Step J: *N*-[2-(Amino)-4-methylcarboxyl]-4-ethyl-3-oxo-4-aza-5α-androst-1-en-17β-acetamide (3-13)

To a solution of 3-10 (0.150 g, 0.417 mmol) and HOAt (0.068 g, 0.501 mmol) in DMF (1.0 mL) was added EDC (0.096 g, 0.501 mmol) and the reaction was stirred at room temperature. After 15 minutes, methyl 3,4-diaminobenzoate (0.104 g, 0.626 mmol) was added and the reaction was heated to 60°C and stirred for 30 minutes. After cooling, the reaction was concentrated and azeotroped with

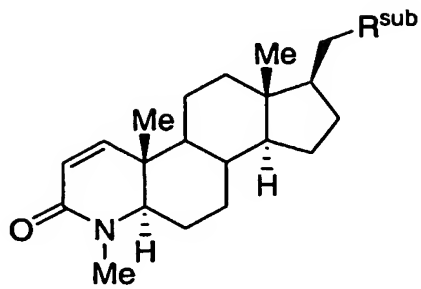
toluene. The residue was purified by chromatography on silica gel (0 to 10% MeOH in CH_2Cl_2) to afford 3-13 as a white solid. MS calculated M+H: 508, found 508.

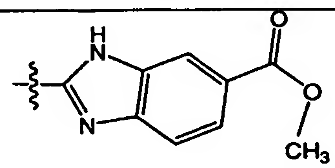
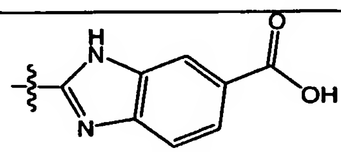
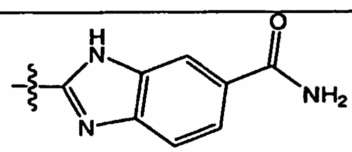
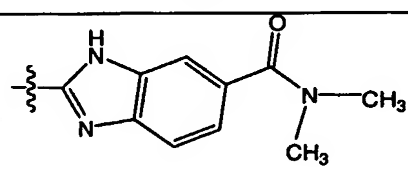
Step K: 17β-[(5-methyl carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one (3-14)

A solution of 3-13 (0.191 g, 0.376 mmol) in acetic acid (0.75 mL) was heated to 130°C in the microwave and stirred for 9 minutes. After cooling, the reaction was concentrated and azeotroped with toluene afford 3-14 as a white solid. MS calculated M+H: 490, found 490.

Examples 32-34 in Table 3 were prepared in a similar manner as Example 31, but using the appropriate amine to generate the carboxamide.

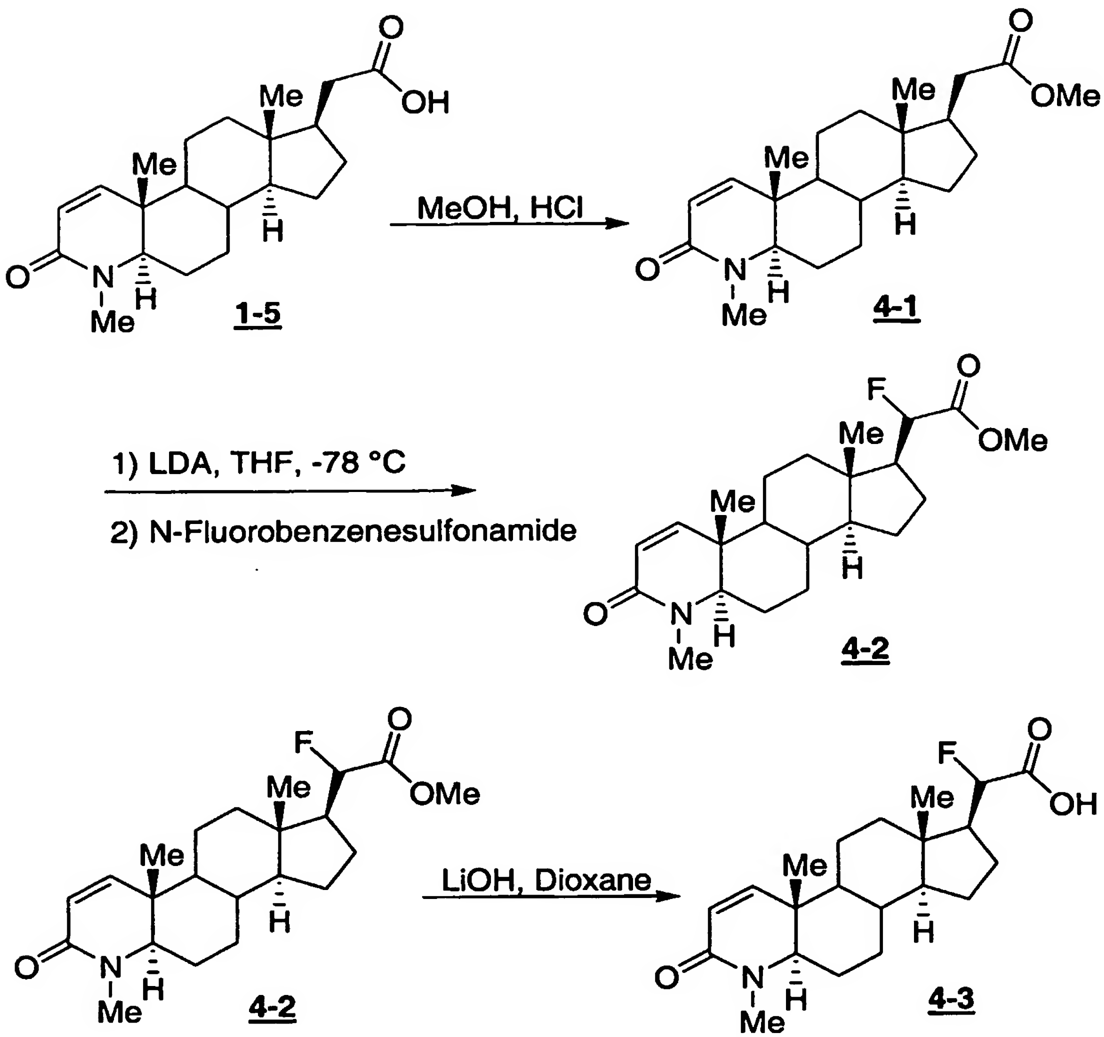
TABLE 3

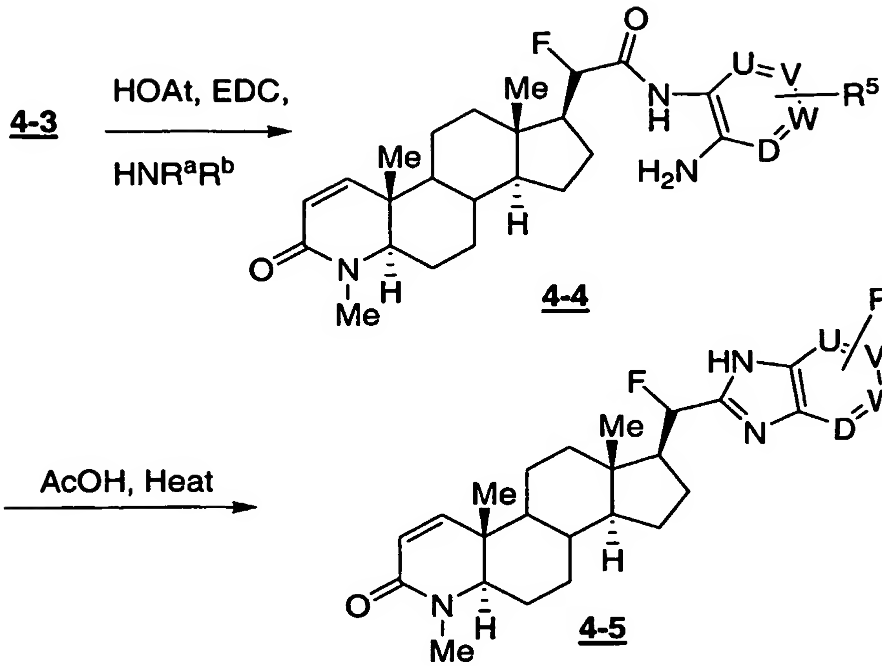


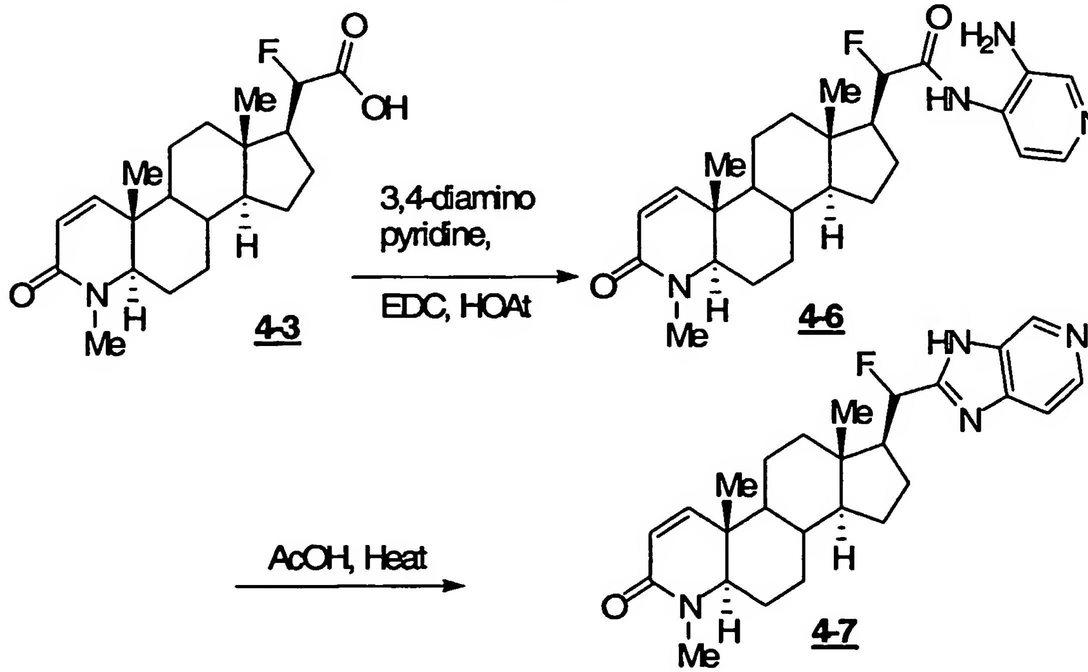
Ex.	R^{sub}	Name	Mass spectrum Measured [M+H]
31		17β-[(5-methyl carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one	489.44
32		17β-[(5-carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one	476.0
33		17β-[(5- carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one	475.0
34		17β-[(5-N,N-dimethyl carboxamido-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one	503.1

The selective androgen receptor modulators (SARMs) of structural formula 4-5 were prepared as outlined in Scheme 4. The starting material was the 17β-acetic acid 1-5 that was prepared in Scheme 1.

Scheme 4


MeOH, HCl
1-5
4-1
1) LDA, THF, -78 °C
2) N-Fluorobenzenesulfonamide
4-2
4-2
LiOH, Dioxane
4-3





Example 35

Step A: 21-Methyl-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetate (4-1)

A solution of 1-5 (3.0 g, 9.1 mmol) in MeOH:AcOH (2:1-22.5 mL) was heated to 55°C and stirred for 18 hours. The reaction was then cooled to room temperature, diluted with CH_2Cl_2 (900 mL), and washed with H_2O and brine, dried ($MgSO_4$) and then concentrated. The residue was purified by

chromatography on silica gel (0-100% EtOAc in hexanes) to afford 4-1 as a white solid. MS calculated M+H: 360, found 360.

Step B: 20-Fluoro-21-methyl-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetate (4-2)

To a solution of 4-1 (0.75 g, 2.8 mmol) in anhydrous THF (11 mL) at -78°C was added hexamethylphosphorous triamide (0.25 mL, 1.39 mmol). Lithium diisopropylamide mono(tetrahydrofuran) complex (2.8 mL, 4.17 mmol, 1.5 M solution in THF) was then added dropwise and the reaction was stirred at – 78°C for 15 minutes. N-fluoro-benzenesulfonamide (1.32 g, 4.27 mmol, dissolved in 1.5 mL of THF) was then added dropwise and the reaction was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl (25 mL), diluted with CH_2Cl_2 (200 mL), washed with brine, dried ($MgSO_4$) and then concentrated. The residue was purified by chromatography on silica gel (0-100% EtOAc in hexanes) to afford 4-2 as a yellow oil. MS calculated M+H: 378, found 378.

Step C: 20-Fluoro-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-acetic acid (4-3)

To a solution of 4-2 (0.79 g, 2.09 mmol) in dioxane (7 mL) at room temperature was added LiOH monohydrate (0.26 g, 6.28 mmol) dissolved in H_2O (2 mL) and the reaction was allowed to stir at room temperature for 18 hours. The reaction was acidified with 1 N HCl to pH 5 and then extracted with CH_2Cl_2 (200 mL), washed with brine, dried ($MgSO_4$) and then concentrated to afford 4-3 as a white solid. MS calculated M+H: 364, found 364.

Step D: *N*-[4-(Amino)pyridin-3-yl]-20-fluoro-4-methyl-3-oxo-4-aza-5α-androst-1-en-17β acetamide (4-6)

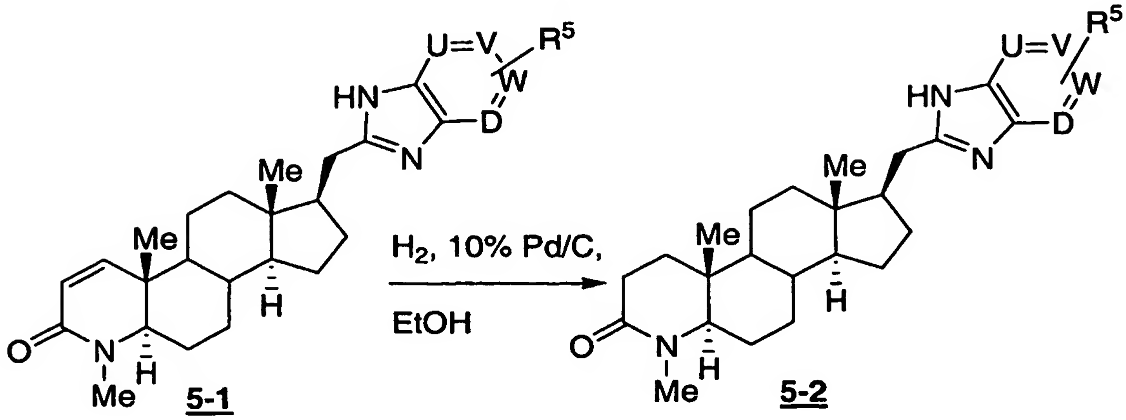
To a solution of 4-3 (0.07 g, 0.19 mmol) and HOAt (0.034 g, 0.25 mmol) in dichloroethane (2.0 mL) was added EDC (0.048 g, 0.25 mmol) and 3,4-diaminopyridine (0.021 g, 0.19 mmol) was added and the reaction was heated to 40 °C and stirred for 12 hours. The reaction was concentrated and the residue was purified by chromatography on silica gel (0-10% MeOH in CH_2Cl_2) to afford 4-6 as a white solid. MS calculated M+H: 455, found 455.

Step E: 20-Fluoro-20-(1*H*-imidazo[4,5-*b*]pyridin-3-yl)-4-methyl-4-aza-5α-androst-1-en-3-one (4-7)

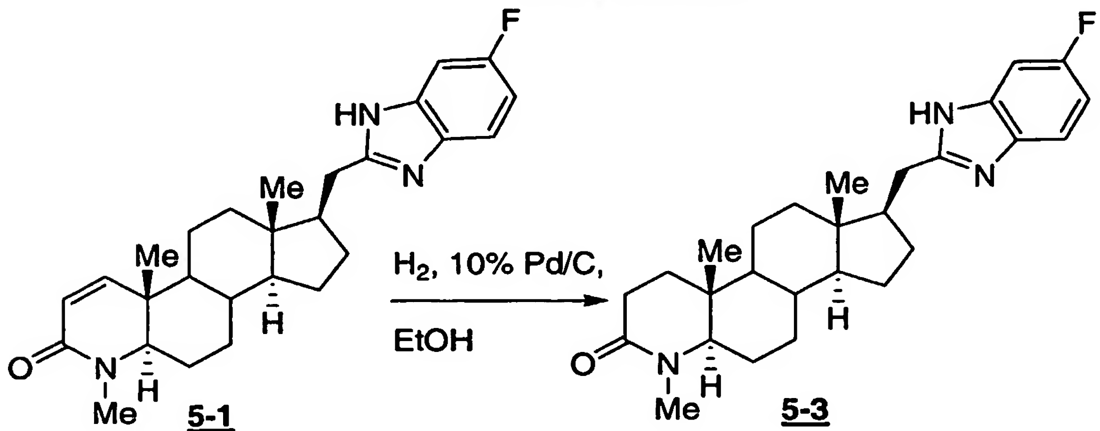
A solution of 4-6 (0.057 g, 0.125 mmol) in acetic acid (0.5 mL) was heated to 180 °C in the microwave and stirred for 45 minutes. After cooling, the reaction was concentrated and azeotroped with toluene to afford 4-7 as a white solid.
MS calculated M+H: 437, found 437.2802.

The selective androgen receptor modulators (SARMs) of structural formula 5-2 were prepared as outlined in Scheme 5. The starting material was the benzimidazole 5-1, which is prepared in Table 1.

Scheme 5



Scheme 5 con't



Example 36:

Step A: 17β-[(5-fluoro-1*H*-benzimidazol-2-yl)methyl]-4-methyl-4-aza-5α-androstan-3-one (5-3)

To a solution of 5-1 (0.07 g, 0.16 mmol) in EtOH (5 mL) at rt was added 10% Palladium on Carbon (0.007 g). The reaction was placed under 45 psi of H_2 using Parr apparatus and was shaken for 18 hours. The reaction was filtered through a pad of celite and the solids were washed with MeOH. The reaction mixture was concentrated to afford 5-3 as a white solid. MS calculated M+H: 438, found 438.

Example 37:

Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of 17β-[(5-carboxylyl-1*H*-benzimidazol-2-yl)methyl]-4-ethyl-4-aza-5α-androst-1-en-3-one, is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard gelatin capsule.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it is understood that the practice of the invention encompasses all of the usual variations, adoptions, or modifications, as being within the scope of the following claims and their equivalents.

ASSAYS

<u>*In Vitro* and *In Vivo* Assays for SARM Activity Identification of Compounds</u>

The compounds exemplified in the present application exhibited activity in one or more of the following assays.

<u>Hydroxylapatite-based Radioligand Displacement</u>
<u>Assay of Compound Affinity for Endogenously Expressed AR</u>

<u>Materials:</u>

Binding Buffer: TEGM (10 mM Tris-HCl, 1 mM EDTA, 10% glycerol, 1 mM beta-mecaptoethanol, 10 mM Sodium Molybdate, pH 7.2)

50% HAP Slurry: Calbiochem Hydroxylapatite, Fast Flow, in 10 mM Tris, pH 8.0 and 1 mM EDTA.

Wash Buffer: 40 mM Tris, pH7.5, 100 mM KCl, 1 mM EDTA and 1 mM EGTA.

95% EtOH

Methyltrienolone, [17α-methyl-^{3}H], (R1881*); NEN NET590

Methyltrienolone (R1881), NEN NLP005 (dissolve in 95% EtOH)

Dihydrotestosterone (DHT) [1,2,4,5,6,7-^{3}H(N)] NEN NET453

Hydroxylapatite Fast Flow; Calbiochem Cat#391947

Molybdate = Molybdic Acid (Sigma, M1651)

<u>MDA-MB-453 cell culture media:</u>

RPMI 1640 (Gibco 11835-055) w/23.8 mM $NaHCO_3$, 2 mM L-glutamine

in 500 mL of complete media	Final conc.
10 mL (1M Hepes)	20 mM
5 mL (200 mM L-glu)	4 mM
0.5 mL (10 mg/mL human insulin) in 0.01 N HCl Calbiochem#407694-S)	10 μg/mL
50 mL FBS (Sigma F2442)	10%
1 mL (10 mg/mL Gentamicin Gibco#15710-072)	20 μg /mL

Cell Passaging

Cells (Hall R. E., et al., European Journal of Cancer, 30A: 484-490 (1994)) are rinsed twice in PBS, phenol red-free Trypsin-EDTA is diluted in the same PBS 1:10. The cell layers are rinsed with 1X Trypsin, extra Trypsin is poured out, and the cell layers are incubated at 37°C for ~ 2 min. The flask is tapped and checked for signs of cell detachment. Once the cells begin to slide off the flask, the complete media is added to kill the trypsin. The cells are counted at this point, then diluted to the appropriate concentration and split into flasks or dishes for further culturing (Usually 1:3 to 1:6 dilution).

Preparation of MDA-MB-453 Cell Lysate

When the MDA cells are 70 to 85% confluent, they are detached as described above, and collected by centrifuging at 1000 g for 10 minutes at 4°C. The cell pellet is washed twice with TEGM (10 mM Tris-HCl, 1 mM EDTA, 10% glycerol, 1 mM beta-mercaptoethanol, 10 mM Sodium Molybdate, pH 7.2). After the final wash, the cells are resuspended in TEGM at a concentration of 10^7 cells/mL. The cell suspension is snap frozen in liquid nitrogen or ethanol/dry ice bath and transferred to −80°C freezer on dry ice. Before setting up the binding assay, the frozen samples are left on ice-water to just thaw (~1 hr). Then the samples are centrifuged at 12,500 g to 20,000 g for 30 min at 4°C. The supernatant is used to
set-up assay right away. If using 50 μL of supernatant, the test compound can be prepared in 50 μL of the TEGM buffer.

Procedure for Multiple Compound Screening

1x TEGM buffer is prepared, and the isotope-containing assay mixture is prepared in the following order: EtOH (2% final concentration in reaction), ^{3}H-R1881 or ^{3}H-DHT (0.5 nM final Conc. in reaction) and 1x TEGM. [eg. For 100 samples, 200 μL (100 x 2) of EtOH + 4.25 μL of 1:10 ^{3}H-R1881 stock + 2300 μL (100 x 23) 1x TEGM]. The compound is serially diluted, e.g., if starting final conc. is 1 μM, and the compound is in 25 μL of solution, for duplicate samples, 75 μL of 4x1 μM solution is made and 3 μL of 100 μM is added to 72 μL of buffer, and 1:5 serial dilution.

25μL of ^{3}H-R1881 trace and 25 μL compound solution are first mixed together, followed by addition of 50 μL receptor solution. The reaction is gently mixed, spun briefly at about 200 rpm and incubated at 4°C overnight. 100 μL of 50% HAP slurry is prepared and added to the incubated reaction which is then vortexed and incubated on ice for 5 to 10 minutes. The reaction mixture is vortexed twice more to resuspend HAP while incubating reaction. The samples in 96-well format are then washed in wash buffer using The FilterMate™ Universal Harvester plate washer (Packard). The washing process transfers HAP pellet containing ligand-bound expressed receptor to Unifilter-96 GF/B filter plate (Packard). The HAP pellet on the filter plate is incubated with 50 μL of MICROSCINT

(Packard) scintillint for 30 minutes before being counted on the TopCount microscintillation counter (Packard). IC_{50}s are calculated using R1881 as a reference.

The compounds, Examples 1-34, found in Tables 1-4, and Examples 35 and 36 were tested in the above assay and found to have an IC_{50} value of 1 micromolar or less.

MMP1 Promoter Suppression, Transient Transfection Assay (TRAMPS)

HepG2 cells are cultured in phenol red free MEM containing 10 % charcoal-treated FCS at 37°C with 5% CO_2. For transfection, cells are plated at 10,000 cells/well in 96 well white, clear bottom plates. Twenty four hours later, cells are co-transfected with a MMP1 promoter-luciferase reporter construct and a rhesus monkey expression construct (50 : 1 ratio) using FuGENE6 transfection reagent, following the protocol recommended by manufacturer. The MMP1 promoter-luciferase reporter construct is generated by insertion of a human MMP1 promoter fragment (-179/+63) into pGL2 luciferase reporter construct (Promega) and a rhesus monkey AR expression construct is generated in a CMV-Tag2B expression vector (Stratagene). Cells are further cultured for 24 hours and then treated with test compounds in the presence of 100 nM phorbol-12-myristate-13-acetate (PMA), used to increase the basal activity of MMP1 promoter. The compounds are added at this point, at a range of 1000nM to 0.03nM, 10 dilutions, at a concentration on 10X, 1/10th volume (example:10 microliters of ligand at 10X added to 100 microliters of media already in the well). Cells are further cultured for an additional 48 hours. Cells are then washed twice with PBS and lysed by adding 70 µL of Lysis Buffer (1x, Promega) to the wells. The luciferase activity is measured in a 96-well format using a 1450 Microbeta Jet (Perkin Elmer) luminometer. Activity of test compounds is presented as suppression of luciferase signal from the PMA-stimulated control levels. EC_{50} and Emax values are reported. Tissue selective androgen receptor modulators of the present invention activate repression typically with submicromolar EC_{50} values and Emax values greater than about 50%.

See Newberry EP, Willis D, Latifi T, Boudreaux JM, Towler DA, "Fibroblast growth factor receptor signaling activates the human interstitial collagenase promoter via the bipartite Ets-AP1 element," Mol. Endocrinol. 11: 1129-44 (1997) and Schneikert J, Peterziel H, Defossez PA, Klocker H, Launoit Y, Cato AC, "Androgen receptor-Ets protein interaction is a novel mechanism for steroid hormone-mediated down-modulation of matrix metalloproteinase expression," J. Biol. Chem. 271: 23907-23913 (1996).

Mammalian Two-Hybrid Assay for the Ligand-induced Interaction of N-Terminus and C-Terminus Domains of the Androgen Receptor (Agonist Mode)

This assay assesses the ability of AR agonists to induce the interaction between the N-terminal domain (NTD) and C-terminal domain (CTD) of rhAR that reflects the *in vivo* virilizing potential mediated by activated androgen receptors. The interaction of NTD and CTD of rhAR is quantified as ligand induced association between a Gal4DBD-rhARCTD fusion protein and a VP16-rhARNTD fusion protein as a mammalian two-hybrid assay in CV-1 monkey kidney cells.

The day before transfection, CV-1 cells are trypsinized and counted, and then plated at 20,000 cells/well in 96-well plates or larger plates (scaled up accordingly) in DMEM + 10% FCS. The next morning, CV-1 cells are cotransfected with pCBB1 (Gal4DBD-rhARLBD fusion construct expressed under the SV40 early promoter), pCBB2 (VP16 -rhAR NTD fusion construct expressed under the SV40 early promoter) and pFR (Gal4 responsive luciferase reporter, Promega) using LIPOFECTAMINE PLUS reagent (GIBCO-BRL) following the procedure recommended by the vendor. Briefly, DNA admixture of 0.05 μg pCBB1, 0.05 μg pCBB2 and 0.1 μg of pFR is mixed in 3.4 μL OPTI-MEM (GIBCO-BRL) mixed with "PLUS Reagent" (1.6 μL, GIBCO-BRL) and incubated at room temperature (RT) for 15 min to form the pre-complexed DNA.

For each well, 0.4 μL LIPOFECTAMINE Reagent (GIBCO-BRL) is diluted into 4.6 μL OPTI-MEM in a second tube and mixed to form the diluted LIPOFECTAMINE Reagent. The pre-complexed DNA (above) and the diluted LIPOFECTAMINE Reagent (above) are combined, mixed and incubated for 15 minutes at room temperature. The medium on the cells is replaced with 40 μL /well OPTI-MEM, and 10 μL DNA-lipid complexes are added to each well. The complexes are mixed into the medium gently and incubated at 37°C at 5% CO_2 for 5 hours. Following incubation, 200 μL /well D-MEM and 13% charcoal-stripped FCS are added, followed by incubation at 37°C at 5% CO_2. After 24 hours, the test compounds are added at the desired concentration(s) (1 nM – 10 μM). Forty eight hours later, luciferase activity is measured using LUC-Screen system (TROPIX) following the manufacturer's protocol. The assay is conducted directly in the wells by sequential addition of 50 μL each of assay solution 1 followed by assay solution 2. After incubation for 40 minutes at room temperature, luminescence is directly measured with 2-5 second integration.

Activity of test compounds is calculated as the E_{max} relative to the activity obtained with 3 nM R1881. Typical tissue-selective androgen receptor modulators of the present invention display weak or no agonist activity in this assay with less than 50% agonist activity at 10 micromolar.

See He B, Kemppainen JA, Voegel JJ, Gronemeyer H, Wilson EM, "Activation function in the human androgen receptor ligand binding domain mediates inter-domain communication with the NH(2)-terminal domain," J. Biol. Chem. 274: 37219-37225 (1999).

A Mammalian Two-Hybrid Assay For Inhibition of Interaction between N-Terminus and C-Terminus Domains of Androgen Receptor (Antagonist Mode)

This assay assesses the ability of test compounds to antagonize the stimulatory effects of R1881 on the interaction between NTD and CTD of rhAR in a mammalian two-hybrid assay in CV-1 cells as described above.

Forty eight hours after transfection, CV-1 cells are treated with test compounds, typically at 10 µM, 3.3 µM, 1 µM, 0.33 µM, 100 nM, 33 nM, 10 nM, 3.3 nM and 1 nM final concentrations. After incubation at 37°C at 5% CO_2 for 10-30 minutes, an AR agonist methyltrienolone (R1881) is added to a final concentration of 0.3 nM and incubated at 37°C. Forty-eight hours later, luciferase activity is measured using LUC-Screen system (TROPIX) following the protocol recommended by the manufacturer. The ability of test compounds to antagonize the action of R1881 is calculated as the relative luminescence compared to the value with 0.3 nM R1881 alone.

Trans-Activation Modulation of Androgen Receptor (TAMAR)

This assay assesses the ability of test compounds to control transcription from the MMTV-LUC reporter gene in MDA-MB-453 cells, a human breast cancer cell line that naturally expresses the human AR. The assay measures induction of a modified MMTV LTR/promoter linked to the LUC reporter gene.

20,000 to 30,000 cells/well are plated in a white, clear-bottom 96-well plate in "Exponential Growth Medium" which consists of phenol red-free RPMI 1640 containing 10%FBS, 4mM L-glutamine, 20mM HEPES, 10ug/mL human insulin, and 20ug/mL gentamicin. Incubator conditions are 37°C and 5% CO_2. The transfection is done in batch mode. The cells are trypsinized and counted to the right cell number in the proper amount of fresh media, and then gently mixed with the Fugene/DNA cocktail mix and plated onto the 96-well plate. All the wells receive 200 Tl of medium + lipid/DNA complex and are then incubated at 37°C overnight. The transfection cocktail consists of serum-free Optimem, Fugene6 reagent and DNA. The manufacturer's (Roche Biochemical) protocol for cocktail setup is followed. The lipid (Tl) to DNA (Tg) ratio is approximately 3:2 and the incubation time is 20 minutes at room temperature. Sixteen to 24 hrs after transfection, the cells are treated with test compounds such that the final DMSO (vehicle) concentration is <3%. The cells are exposed to the test compounds for 48 hours. After 48 hours, the cells are lysed by a Promega cell culture lysis buffer for 30-60 minutes and then the luciferase activity in the extracts is assayed in the 96-well format luminometer.

Activity of test compounds is calculated as the E_{max} relative to the activity obtained with 100 nM R1881.

See R.E. Hall, et al., "MDA-MB-453, an androgen-responsive human breast carcinoma cell line with high androgen receptor expression," Eur. J. Cancer, 30A: 484-490 (1994) and R.E. Hall, et al., "Regulation of androgen receptor gene expression by steroids and retinoic acid in human breast-cancer cells," Int. J. Cancer., 52: 778-784 (1992).

In Vivo Prostate Assay

Male Sprague-Dawley rats aged 9-10 weeks, the earliest age of sexual maturity, are used in prevention mode. The goal is to measure the degree to which androgen-like compounds delay the rapid deterioration (~-85%) of the ventral prostate gland and seminal vesicles that occurs during a seven day period after removal of the testes (orchiectomy [ORX]).

Rats are orchiectomized (ORX). Each rat is weighed, then anesthetized by isoflurane gas that is maintained to effect. A 1.5 cm anteroposterior incision is made in the scrotum. The right testicle is exteriorized. The spermatic artery and vas deferens are ligated with 4.0 silk 0.5cm proximal to the testicle. The testicle is freed by one cut of a small surgical scissors distal to the ligation site. The tissue stump is returned to the scrotum. The same is repeated for the left testicle. When both stumps are returned to the scrotum, the scrotum and overlying skin are sutured closed with 4.0 silk. For Sham-ORX, all procedures excepting ligation and scissors cutting are completed. The rats fully recover consciousness and full mobility within 10-15 minutes.

A dose of test compound is administered subcutaneously or orally to the rat immediately after the surgical incision is sutured. Treatment continues for an additional six consecutive days.

Necropsy and Endpoints

The rat is first weighed, then anesthetized in a CO_2 chamber until near death. Approximately 5ml whole blood is obtained by cardiac puncture. The rat is then examined for certain signs of death and completeness of ORX. Next, the ventral portion of the prostate gland is located and blunt dissected free in a highly stylized fashion. The ventral prostate is blotted dry for 3-5 seconds and then weighed (VPW). Finally, the seminal vesicle is located and dissected free. The ventral seminal vesicle is blotted dry for 3-5 seconds and then weighed (SVWT).

Primary data for this assay are the weights of the ventral prostate and seminal vesicle. Secondary data include serum LH (luteinizing hormone) and FSH (follicle stimulating hormone), and possible serum markers of bone formation and virilization. Data are analyzed by ANOVA plus Fisher PLSD post-hoc test to identify intergroup differences. The extent to which test compounds inhibit ORX-induced loss of VPW and SVWT is assessed.

In Vivo Bone Formation Assay:

Female Sprague-Dawley rats aged 7-10 months are used in treatment mode to simulate adult human females. The rats have been ovariectomized (OVX) 75-180 days previously, to cause bone loss and simulate estrogen deficient, osteopenic adult human females. Pre-treatment with a low dose of a powerful anti-resorptive, alendronate (0.0028mpk SC, 2X/wk) is begun on Day 0. On Day 15, treatment with test compound is started. Test compound treatment occurs on Days 15-31 with necropsy on Day 32. The goal is to measure the extent to which androgen-like compounds increase the amount of bone formation, shown by increased fluorochrome labeling, at the periosteal surface.

In a typical assay, nine groups of seven rats each are studied.

On Days 19 and 29 (fifth and fifteenth days of treatment), a single subcutaneous injection of calcein (8mg/kg) is given to each rat.

Necropsy and Endpoints

The rat is first weighed, then anesthetized in a CO_2 chamber until near death. Approximately 5mL whole blood is obtained by cardiac puncture. The rat is then examined for certain signs of death and completeness of OVX. First, the uterus is located, blunt dissected free in a highly stylized fashion, blotted dry for 3-5 seconds and then weighed (UW). The uterus is placed in 10% neutral-buffered formalin. Next, the right leg is disarticulated at the hip. The femur and tibia are separated at the knee, substantially defleshed, and then placed in 70% ethanol.

A 1-cm segment of the central right femur, with the femoral proximal-distal midpoint ats center, is placed in a scintillation vial and dehydrated and defatted in graded alcohols and acetone, then introduced to solutions with increasing concentrations of methyl methacrylate. It is embedded in a mixture of 90% methyl methacrylate: 10% dibutyl phthalate, that is allowed to polymerize over a 48-72 hours period. The bottle is cracked and the plastic block is trimmed into a shape that conveniently fits the vice-like specimen holder of a Leica 1600 Saw Microtome, with the long axis of the bone prepared for cross-sectioning. Three cross-sections of 85μm thickness are prepared and mounted on glass slides. One section from each rat that approximates the midpoint of the bone is selected and blind-coded. The periosteal surface of each section is assessed for total periosteal surface, single fluorochrome label, double fluorochrome label, and interlabel distance.

Primary data for this assay are the percentage of periosteal surface bearing double label and the mineral apposition rate (interlabel distance(μm)/10d), semi-independent markers of bone formation. Secondary data include uterus weight and histologic features. Tertiary endpoints can include serum markers of bone formation and virilization. Data are analyzed by ANOVA plus Fisher PLSD post-hoc test to identify intergroup differences. The extent to which test compounds increase bone formation endpoint are assessed.